LUDWIG CANCER RESEARCH	**Study Protocol**	**LUD2013-006**	**US-IND# 118511**
	Amendment 5	**Final**	**14-APR-2017**

Protocol Title
Phase 2 study to Evaluate the Clinical Efficacy and Safety of MEDI4736 in Patients with Glioblastoma (GBM)

Objectives and Synopsis

This is an open-label, non-randomized, multicenter Phase 2 study of MEDI4736 with three non-comparative cohorts:

Cohort A: 37 Subjects with newly diagnosed unmethylated MGMT GBM will receive MEDI4736 every 2 weeks (Q2W) for up to 12 months in combination with standard radiotherapy. The cohort will be started on 10 mg/kg intravenous (IV), which was the current recommended Phase 2 dose (RP2D) based on previous Phase 1 monotherapy data. Since there are no safety data available for this combination, the first 6 subjects will be evaluated for DLTs for 10 weeks to determine if the dose for this cohort should be lowered to 3 mg/kg or 1 mg/kg, which may add up to 12 subjects, for a total of 49 subjects. The ***Primary Objective*** is to evaluate the clinical efficacy as measured by the Overall Survival (OS) rate at 12 months.

Cohort B: 30 bevacizumab-naïve subjects with recurrent GBM receive MEDI4736 Q2W for up to 12 months as monotherapy at 10 mg/kg IV infusion, which is the current RP2D based on previous Phase 1 monotherapy data. The ***Primary Objective*** is to evaluate the clinical efficacy as measured by progression-free survival rate at six months (PFS-6).

Per Protocol Amendment 2, two additional cohorts will be added to the study. The 2 additional cohorts will have the same study population criteria as Cohort B but will receive the following treatments:

- Cohort B2 (n=32): MEDI4736 (10 mg/kg Q2W) + bevacizumab (10 mg/kg Q2W)
- Cohort B3 (n=32): MEDI4736 (10 mg/kg Q2W) + bevacizumab (3 mg/kg Q2W).

Cohort C: 17 bevacizumab-refractory subjects with recurrent GBM receive MEDI4736 Q2W for up to 12 months in combination with continued bevacizumab at 10 mg/kg Q2W. MEDI4736 will be administered prior to bevacizumab and start at 10 mg/kg IV, the current RP2D based on previous Phase 1 monotherapy data. Since there is no safety data for this combination, the first 6 subjects will be evaluated for DLTs for 6 weeks to determine if the MEDI4736 dose for this cohort should be lowered to 3 mg/kg or 1 mg/kg, which may add up to 12 subjects, for a total of 29 subjects. The ***Primary Objective*** is to evaluate the clinical efficacy as measured by the Overall Survival (OS) rate at 6 months (OS-6).

In **all Cohorts**, the ***Secondary Objectives*** are the evaluation of safety/tolerability and clinical efficacy as measured by median progression-free survival, median overall survival and radiographic response, and quality of life (QoL) by the European Organization for Research and Treatment of Cancer quality of life questionnaire with a brain cancer module (EORTC QLQ-C30/BN20). The ***Exploratory Objectives*** are the evaluation of subject neurologic function using the Neurologic Assessment in Neuro-Oncology (NANO) scale, as well as the correlative biomarkers.

Per Amendment 3, optional treatment extension beyond the 1-year study (Core Study) is available for subjects who complete 51 weeks of treatment on Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Appendix 8.8 for details.
Per Amendment 4, the collection of samples for MEDI4736 PK, ADA, sPD-L1, and circulating soluble factors was removed.

Sponsor: Ludwig Institute for Cancer Research, Ltd.	**Study Chair:** [redacted]
Sponsor Representative Signature & Date	Study Chair Signature & Date

Confidentiality Statement

Table of Contents

1 Background

1.1 Glioblastoma

Glioblastoma (GBM), the most common primary malignant CNS tumor, remains a major unmet oncologic need. Current standard therapy including aggressive surgery, brain irradiation and temozolomide chemotherapy, yields a 15-month median overall survival while exposing patients to significant potential neurologic morbidity and detrimental impact on quality of life.(1) Following progression, no therapy has been identified that durably prolongs survival. Clinical studies evaluating targeted molecular inhibitors have consistently yielded disappointing results (2) while bevacizumab, a monoclonal antibody targeting VEGF, improves progression-free survival and radiographic response rate, but has not been shown to meaningfully improve survival. (3, 4) Furthermore, all patients ultimately progress on bevacizumab, and then typically succumb to progressive disease within a few months. No therapeutic approach has had any impact on outcome for bevacizumab-resistant, glioblastoma patients (5) although bevacizumab continuation beyond initial progression appears to be associated with minimal benefit.(6) Innovative treatment strategies that improve outcome while preserving neurologic integrity for glioblastoma patients are desperately needed.

1.1.1 Unmethylated MGMT Glioblastoma

Approximately 2/3 of GBM patients have tumors that express significant levels of methylguanine methyltransferase (MGMT) due to lack of methylation of the promoter.(7) MGMT is a ubiquitous DNA repair enzyme whose expression is enhanced in some cancers, including the majority of GBM patients. These patients have been shown to derive minimal benefit from the addition of temozolomide to standard radiation therapy. Specifically in a Phase 3 study, subjects with unmethylated MGMT tumors who received radiation alone had median progression-free and overall survivals of 4.4 months and 11.8 months compared to 5.3 months and 12.7 months for those who received temozolomide and radiation.(8) The addition of temozolomide increased both PFS and OS for these subjects by less than one month, and was also associated with more adverse events including neutropenia, thrombocytopenia and infections. Nonetheless, unmethylated MGMT GBM patients are routinely offered standard of care treatment with temozolomide due to lack of more effective treatment options, and because their outcome is otherwise so poor. There is a clear need to develop new treatment approaches for unmethylated MGMT GBM patients.

1.2 PD-1 and PD-L1

Programmed Death-1 (PD-1, CD279) is a member of the immunoglobulin superfamily (IGSF) of molecules involved in regulation of T cell activation. PD-1 acquired its name 'programmed death' when it was identified in 1992 as a gene upregulated in T cell hybridoma undergoing cell death.(9) The structure of PD-1 is composed of one IGSF domain, a transmembrane domain, and an intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).(10-12) PD-1 has two binding partners: PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273), distant relatives of the B7-1 and B7-2 molecules. PD-L1, discovered in 1999, is expressed quite broadly, on both hematopoietic and non-hematopoietic lineages.(13-15) It is found on T cells, B cells, macrophages, NK cells, DCs, and mast cells.(16) It has also been described on peripheral tissues including cardiac

endothelium, lung, small intestine, keratinocytes, islet cells of the pancreas, and syncytiotrophoblasts in the placenta as well as a variety of tumor cell types including GBM.(15-32) PD-L1 is constitutively expressed on many hematopoietic cells, but may be upregulated in hematopoietic and non-hematopoietic cells.(33) Regulation of PD-L1 is mediated, in part, by type I and type II interferons. PD-L2 was identified in 2001.(34, 35) Its expression is far more restricted and is confined to hematopoietic cells.(36)

Engagement of PD-1 on T cells inhibits activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T cell function.(13, 37-41) Inhibitory signaling by PD-1 is thought to depend upon the cytosolic ITSM domain, which associates with phosphatases SHP-1 and SHP-2.(42, 43) While CTLA-4 and PD-1 are both inhibitory receptors, they fulfill distinct roles and mediate their effects through distinct mechanisms.(44) For example, PD-1 inhibits activation of the serine threonine kinase Akt via its effect on the phosphoinositide 3-kinase (PI3K) pathway, whereas CTLA-4 inhibits Akt in a PI3K independent manner.(38, 42, 45) Studies of PD-1 -/- knockout and PD-L -/- knockout mice support a unique role for PD-1: PD-L interaction in mediating peripheral tolerance and preventing autoimmunity.(28) The phenotype of the PD-1-/- knockout mouse depends upon the genetic background, but manifestations of spontaneous autoimmunity have been reported, including dilated cardiomyopathy and glomerulonephritis.(46, 47)

Targeting Programmed Death-1 (PD-1) and its ligand, PD-L1, has demonstrated promising anti-tumor activity among some advanced solid tumor cancer subjects (6, 48, 49) and growing data implicates PD-1/PD-L1 signaling as a significant contributor to immunosuppression in glioblastoma. PD-1 is expressed by many glioblastoma infiltrating lymphocytes (29) while PD-L1 is expressed by 61-100% of glioblastoma tumors.(17, 19, 20, 23) PD-L1 expression in a formalin-fixed, paraffin-embedded tissue microarray of 83 glioblastoma tumors revealed that 85% express PD-L1 in over 80% of the tumor cells (D. Reardon, M.D., personal communication). Furthermore, loss of the PTEN tumor suppressor gene, which occurs in 40-50% of GBM tumors, leads to increased transcription and expression of PD-L1 in glioblastoma.(23) Inhibition of PD-1 in an immunocompetent, orthotopic preclinical GBM model was recently demonstrated to improve survival when administered with radiotherapy.(50) Additional preclinical experiments involving an immunocompetent, orthotopic murine glioblastoma model revealed that 25% of animals treated with a murine anti-PD-L1 monoclonal antibody remained alive for over 140 days with no evidence of tumor (control mice uniformly died within 30 days) (D. Reardon, M.D., unpublished data). These aggregate findings indicate that PD-1/PD-L1 is an attractive and important therapeutic target in glioblastoma.

1.3 MEDI4736

MEDI4736 is briefly described in this section. Refer to the current Investigator's Brochure for complete and current information.

MEDI4736 is a human immunoglobulin G1 kappa monoclonal antibody (MAb) directed against human PD-L1. MEDI4736 has an overall molecular weight of approximately 149 kDa, including N-linked oligosaccharides. The antibody is composed of 2 identical heavy chains of approximately 49,670 Da each, and 2 identical light chains of approximately 23,390 Da each. The fragment crystallizable (Fc) domain of MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and

the Fcm receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC). (51) Subsequent to this triple mutation, the anticipated lack of MEDI4736-mediated ADCC and complement dependent cytotoxicity were confirmed using cell based functional assays. MEDI4736 is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and cluster of differentiation (CD) 80 receptors.

1.3.1 Summary of MEDI4736 Nonclinical Experience

Nonclinical data with MEDI4736 suggest that targeting PD-L1 with a biologic agent could be an effective antitumor therapy. MEDI4736 is a human monoclonal antibody that selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and CD80. PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses by delivering inhibitory signals to T cells through the PD-1 and CD80 receptors. Blockade of PD-L1 with MEDI4736 relieved PD-L1-mediated suppression of human T-cell activation in vitro. In a xenograft model, MEDI4736 inhibited human tumor growth via a T-cell dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in >50% of treated mice when given in combination with chemotherapy.

1.3.2 Summary of MEDI4736 Clinical Experience

The first-time-in-human (FTIH) trial, study CD-ON-MEDI4736-1108 (NCT01693562), currently being conducted by MedImmune, is a multicenter, open-label study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors. The study includes a standard 3+3 dose-escalation phase followed by an expansion phase in melanoma, CRC, and NSCLC. Dose escalation began enrollment at 0.1 mg/kg administered by intravenous infusion every 2 weeks. Escalation continued at dose levels of 0.3, 1, 3, and 10 mg/kg or until a maximum tolerated dose (MTD) or optimal biologic dose (OBD) was determined. Once an MTD or OBD was determined, subjects were enrolled in each expansion cohort to further evaluate the safety and preliminary antitumor activity of MEDI4736.

According to the Investigator's Brochure (Edition 6.0, Issue date: 28Mar2014), a total of 198 subjects have been treated with at least one dose of MEDI4736 (ranging from 1 to 27 doses) in study CD-ON-MEDI4736-1108. Twenty-one subjects have been enrolled in the following dose-escalation cohorts: 4 subjects in each of the 0.1, 0.3, and 1 mg/kg every 2 weeks (Q2W) cohorts; 3 subjects in the 3 mg/kg Q2W cohort, and 6 subjects in the 15 mg/kg Q3W cohort. A total of 177 subjects have received MEDI4736 10 mg/kg Q2W which has been selected for further evaluation in the dose expansion phase and is the current recommended Phase 2 dose (RP2D). This includes subjects receiving 10 mg/kg Q2W from both the dose escalation and dose expansion phases. Among the 177 subjects, the most frequently reported (≥ 10% of subjects) treatment-emergent adverse events (TEAEs) regardless of grade or causality were fatigue, dyspnea, nausea, constipation, and decreased appetite. The majority of TEAEs were Grades 1 to 2 in severity and manageable by the general treatment guidelines as described in the current MEDI4736 study protocol and Appendix 8.6. The Grade 3 or higher TEAEs occurring in 2 or more subjects included dyspnea, dehydration, abdominal pain, fatigue, sepsis, increased aspartate aminotransferase, increased gamma-glutamyltransferase, hyperbilirubinemia, back pain, pulmonary embolism, respiratory failure, hypotension, and "progression of disease" (verbatim term). Treatment-related TEAEs (all grades) occurring in 2 or more subjects were fatigue,

nausea, dyspnea, diarrhea, vomiting, pyrexia, myalgia, hypothyroidism, decreased appetite, dizziness, cough, pruritus, rash, abdominal pain, increased aspartate aminotransferase, arthralgia, asthenia, influenza-like illness, edema peripheral, increased alanine aminotransferase, headache, and dry skin.

The SAEs reported for 3 or more subjects were dyspnea, dehydration, abdominal pain, and sepsis. Four subjects had treatment-related SAEs: arthralgia (1 subject); pleural effusion and pneumonitis (both in the same subject); muscular weakness and "rule out cord compression" (verbatim term) (both in the same subject); and ataxia (1 subject). For the entire study population, none of the deaths or TEAEs resulting in discontinuation of MEDI4736 were considered related to MEDI4736. No dose-limiting toxicities (DLTs) have been reported.

Partial efficacy data is also available for this FTIH trial, study CD-ON-MEDI4736-1108 (NCT01693562). Tumor assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines (52) with modifications for subjects in the dose-expansion phase. Of the 177 subjects treated with MEDI4736 10 mg/kg Q2W, 77 have had at least one post-baseline disease assessment as of 18Feb2014. Four subjects (5.2%) had a best response of PR (unconfirmed). In addition, 36 subjects (46.8%) had stable disease, 20 subjects (26.0%) had confirmed progressive disease (PD), 14 subjects (18.2%) had unconfirmed PD, and 3 subjects (3.9%) were not evaluable.

There are 4 additional ongoing clinical studies of MEDI4736 (1 with MEDI4736 as monotherapy and 3 as combination therapy), with limited safety data available. Of the available safety data, there have been no DLTs or deaths reported among 8 additional subjects treated with MEDI4736 monotherapy. As of May 13, 2014, safety data from subjects treated with MEDI4736 and tremelimumab combination include 1 DLT of Grade 3 colitis and 1 death due to myasthenia gravis, both with a causal relationship to the treatment combination.

Updated safety data for MEDI4736 will be made available to the Investigators prior to starting this study. It is expected that the clinical experience with MEDI4736 from other clinical trials will increase rapidly and frequently during the course of this study. Hence, relevant safety data will be communicated to the Investigators via IB updates and safety reports, while this section (Section 1.3.2) will not, or less frequently, be amended.

1.4 Temozolomide Chemoradiotherapy for Newly Diagnosed GBM

Temozolomide (TMZ) is an alkylating agent that induces autophagy, apoptosis and senescence in GBM cells.(53) A meta-analysis of studies evaluating adjuvant nitrosourea therapy for GBM several years ago initially demonstrated the benefit of alkylator chemotherapy for GBM as reflected by a modest survival benefit among treated subjects (6% to 10% increase in 1-year survival). (54, 55) In a large, randomized Phase 3 study conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) among newly diagnosed GBM subjects, the role of radiotherapy (RT) alone (60 Gy over 6 weeks) was compared to RT and concomitant daily temozolomide 75 mg/m2/day, followed by adjuvant temozolomide 150 to 200 mg/m2/day for 5 consecutive days out of every 28-day cycle, for 6 cycles. The results of this study demonstrated that the addition of temozolomide chemotherapy to radiation therapy prolonged median overall survival from 12.1 to 14.6 months for newly-diagnosed GBM subjects.(56) In addition, the proportion of surviving subjects in the

temozolomide group at 2 years was 26.5% compared to only 10.4% among subjects treated with RT-alone group. Longer term follow-up of this study confirmed persistent survival benefit associated with temozolomide administration including a median survival of 9.8% at 5 years for the temozolomide group, compared to only 1.9% among the RT recipients [hazard ratio 0.6; 95% confidence interval: 0.5-0.7; P < .0001].(1) Based on these results, the addition of temozolomide to RT was approved by the US FDA for newly diagnosed GBM patients in 2005. Although the approved dosing for temozolomide specifies up to 6 cycles (28-day cycle) of adjuvant therapy following the concomitant phase, standard of care treatment in some regions has evolved to include temozolomide treatment for 12 adjuvant cycles or longer.

In a companion study, an analysis of the methylation status of the O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter among tumor specimens from subjects of the EORTC/NCIC study were evaluated. This retrospective analysis confirmed that subjects with a methylated MGMT promoter achieved a significantly improved outcome compared to those with an unmethylated MGMT promoter. Specifically, subjects with MGMT methylated tumors who received temozolomide had a median survival was 21.7 months and 2-year survival rate of 46%; in contrast, subjects with unmethylated MGMT tumors who received temozolomide had a median survival of 12.7 months and a 2-year survival rate of 13.8%. (8) Among subjects who had an unmethylated MGMT promoter, the addition of temozolomide was associated with a nominal 0.8 month increase in median overall survival compared to radiation therapy.(1) Importantly, methylation of the MGMT promoter occurs only in 30-45% of newly diagnosed GBM patients.(7, 8) The prognostic value of tumor MGMT promoter methylation status was recently confirmed in RTOG 0525, a large prospective study that randomized newly diagnosed GBM subjects to standard 5-day adjuvant temozolomide versus dose dense adjuvant temozolomide administered for 21 days of each 28 day cycle. In this study, which required prospective determination of tumor MGMT status for eligibility, there was no difference in overall survival or progression-free survival between the study arms, but subjects who had a methylated MGMT promoter had significantly better outcome. Specifically, MGMT methylation was associated with improved median overall survival (21.2 vs 14.0 months; HR 1.74; p<0.001) and median progression-free survival (8.7 vs 5.7 months; HR, 1.63; p<0.001).(57)

Although temozolomide provides a modest benefit for newly diagnosed glioblastoma subjects, its value is particularly limited among subjects with unmethylation of the MGMT tumor promoter. Nonetheless, due to lack of better available therapies, temozolomide with radiation, followed by adjuvant temozolomide remains the standard of care for newly diagnosed GBM patients, regardless of tumor MGMT promoter status.

TMZ is marketed by Merck under the name Temodar® Details of clinical studies and the safety profile of temozolomide are documented in the Temodar® prescribing information.

1.5 Therapy for Recurrent GBM

Progression among newly diagnosed GBM patients treated with current standard therapy is essentially inevitable, and the median progression-free survival associated with temozolomide chemoradiotherapy is only 5.5 months among those with MGMT unmethylated tumors.(57) Conventional chemotherapy for recurrent GBM patients has had limited benefit. Phase 2 trials of temozolomide for recurrent GBM treated initially with radiotherapy alone demonstrate ORR rates of only 5%, stable disease in 40% of subjects, and a 6-month PFS rate of approximately

21%. (58-60) Administration of protracted, daily temozolomide schedule has also demonstrated poor outcome among subjects who have progressed after standard 5-day temozolomide.(61) Other agents such as carmustine, lomustine, carboplatin, etoposide, irinotecan, and procarbazine used in chemotherapy combinations produce low response rates and no significant survival benefit.(62)

Significant insight into the molecular pathogenesis of GBM has been achieved in recent years,(63-68) and these findings have stimulated significant interest in evaluating therapeutics aimed at blocking key mediators of dysregulated cell signaling pathways in clinical trials.(2, 69, 70) Nonetheless, despite multiple trials incorporating a wide array of targeted inhibitors, results of these efforts have been consistently unsuccessful.(71) A variety of factors have been implicated in the poor response of salvage therapies for recurrent GBM patients, including reduced drug delivery as a result of the blood-brain barrier, intrinsic resistance to cytotoxic chemotherapy, complex and redundant mechanisms of dysregulated cell signaling, heterogeneity within and across tumors, tumor hypoxia, pharmacokinetic interactions with anti-convulsant therapies that diminish chemotherapy exposure, and a relatively low tumor cell growth fraction.

Glioblastoma is one of the most angiogenic of cancers and the role of angiogenic factors such as vascular endothelial growth factor (VEGF) has been well established.(72-74) Bevacizumab, a VEGF inhibitor, has been evaluated as a single agent in subjects with recurrent GBM. Among recurrent GBM subjects, bevacizumab has been associated with durable radiographic responses. Specifically, a randomized, multi-center Phase 2 study noted a 4.2 month median duration of response,(3) while a single arm study conducted at the National Cancer Institute observed an objective response rate of 19.6% and a 3.9 month median duration of response.(4) Based on these studies, bevacizumab was approved in the US for treatment of patients with recurrent GBM,(75) but approval was not achieved in other countries.(76) Nonetheless, essentially all recurrent patients ultimately progress following bevacizumab salvage therapy and to date, no effective therapy has been identified after progression on bevacizumab.(77)

Reardon et al. retrospectively analyzed the outcomes of subjects who received subsequent therapy after progression to evaluate the efficacy of bevacizumab regimens against recurrent GBM in five clinical trials with similar eligibility, treatment, and assessment criteria.(78) The results of this pooled analysis suggested bevacizumab continuation beyond initial progression modestly improves median overall survival and overall survival at 6 months, compared with a non-bevacizumab regimen (5.9 months and 49.2% vs 4 months and 29.5%). Bevacizumab continuation was identified as independent predictor of improved overall survival (HR = 0.64; p = 0.04).

Bevacizumab continuation beyond progression in GBM may be necessary to prevent increased tumor-associated cerebral edema or rapid tumor re-growth, reported as a “rebound” phenomenon by Zuniga et al.(79) In their retrospective review of 40 subjects refractory to bevacizumab therapy, 27.5% exhibited rebound progression with a median overall survival of only 6.8 weeks. Of 3 subjects who were restarted on bevacizumab treatment after rebound progression, 2 exhibited a partial response, and the OS was extended to 21.3 weeks. The study suggests abrupt discontinuation of bevacizumab after progression often leads to a dramatic rebound phenomenon and rapid clinical decline.

Based on data from Reardon et al.(78) and Zuniga et al.,(79) evaluating bevacizumab continuation in combination with new agents in subjects progressing on bevacizumab warrants further prospective investigation.

Importantly, the toxicity profiles of bevacizumab and immune checkpoint inhibiting therapeutics are non-overlapping; thus the combination of bevacizumab continuation and MEDI-4736 is expected to be well tolerated. In support of this expectation, preliminary data demonstrate that the combination of bevacizumab plus ipilimumab among advanced melanoma subjects has been well tolerated and without unexpected toxicity or increased toxicity compared to that noted with administration of either agent alone.(80)

2 Study Rationale

Outcome among both newly diagnosed as well as recurrent GBM patients remains poor and novel therapeutic approaches are clearly needed. Targeting Programmed Death-1 (PD-1) and its ligand, PD-L1, have demonstrated promising anti-tumor activity among other challenging solid tumors,(6, 81) and growing data implicate PD-1/PD-L1 signaling as a significant contributor to immunosuppression in glioblastoma. PD-1 is expressed by many glioblastoma infiltrating lymphocytes (29) while PD-L1 is expressed by 61-100% of glioblastoma tumors.(17, 19, 20) PD-L1 expression in a formalin-fixed, paraffin-embedded tissue microarray of 83 glioblastoma tumors revealed that 85% express PD-L1 in over 80% of the tumor cells (D. Reardon, M.D., personal communication). Furthermore, loss of the PTEN tumor suppressor gene, which occurs in 40-50% of GBM tumors, leads to increased transcription and expression of PD-L1 in glioblastoma.(23) Inhibition of PD-1 in an immunocompetent, orthotopic preclinical GBM model was recently demonstrated to improve survival when administered with radiotherapy.(50) Additional preclinical experiments involving an immunocompetent, orthotopic murine glioblastoma model revealed that 25% of animals treated with a murine anti-PD-L1 monoclonal antibody remained alive for over 140 days with no evidence of tumor (control mice uniformly died within 30 days) (D. Reardon, M.D., unpublished data). These aggregate findings indicate that PD-1/PD-L1 is an attractive and important therapeutic target in GBM.

The current study is thus designed to evaluate the immunogenicity, safety and clinical efficacy of MEDI4736 among both newly diagnosed and recurrent glioblastoma subject subsets. The results of this study will provide important insight to optimally guide development of MEDI4736 for this indication.

As discussed in Section 1.3.2, 10 mg/kg is the RP2D of MEDI4736 for other cancer indications based upon completed dose escalation and expansion portions of the FTIH Phase 1 study. It is anticipated that this dose will be suitable for all three cohorts, however, as there are no safety data for MEDI4736 in combination with radiation or bevacizumab, the option for dose de-escalations to 3 mg/kg and 1 mg/kg is included for Cohorts A and C. In all cohorts, the first study drug administration for the first subject and the second subject will be separated by at least 1 week.

In Cohort A, which consists of newly diagnosed glioblastoma subjects with MGMT unmethylated tumors, we will evaluate MEDI4736 when administered with standard radiotherapy after maximum safe resection. The rationale for this approach is that radiation induces cell death with release of tumor antigens that could potentiate the immune-mediated anti-tumor activity of MEDI4736.(82)

The standard combination of temozolomide with radiotherapy will not be administered to subjects in Cohort A because MGMT unmethylated glioblastoma subjects experience no survival benefit and increased systemic toxicity as previously discussed, and because temozolomide may limit anti-tumor immune responses following anti-PD-L1 therapy.

The toxicities reported with MEDI4736 do not appear to overlap with those associated with standard radiotherapy for newly diagnosed glioblastoma subjects. Thus, it is anticipated that a dose of 10 mg/kg will be well tolerated when combined with standard radiotherapy. Toxicity management and dose adjustments will be followed according to local approved radiotherapy

guidelines and Appendix 8.6 for MEDI4736. Although bevacizumab received FDA accelerated approval for recurrent glioblastoma patients based on radiologic response,(75) clinical benefit to support full approval has not been demonstrated. In addition, bevacizumab failed to improve overall survival in two placebo-controlled, randomized Phase 3 studies among newly diagnosed glioblastoma subjects.(83, 84) Furthermore, all subjects progress following bevacizumab therapy and then typically succumb within a few months from fulminate, progressive disease, regardless of whether bevacizumab is continued. Despite many attempts, no therapies have been of benefit following the emergence of bevacizumab resistance.(77, 78, 85) Thus, the identification of active agents for recurrent glioblastoma patients remains a major unmet need in oncology today.

This study will evaluate two cohorts of subjects with recurrent glioblastoma; MEDI4736 as monotherapy in bevacizumab naïve subjects (Cohort B) and MEDI4736 combined with bevacizumab continuation in bevacizumab refractory subjects (Cohort C). As described in Section 1.5, the continuation of bevacizumab following progression may alleviate tumor-associated rebound edema and mass effect thereby potentiating anti-tumor immune response from MEDI4736. Due to limited safety data on bevacizumab and anti-PD-L1 combination treatment, Cohort C will begin with a 3+3 subject safety run-in observing subjects in sequential groups of 3 to evaluate DLTs. De-escalations to 3 mg/kg and 1 mg/kg of MEDI4736 will be made as necessary. Toxicity management and dose adjustments will be followed according to local approved bevacizumab regulatory prescribing information and Appendix 8.6 for MEDI4736. As discussed in Section 1.5, the toxicity profiles of bevacizumab and immune checkpoint inhibiting therapeutics are non-overlapping; thus the combination of bevacizumab continuation and MEDI4736 is expected to be well tolerated.

Evidence of anti-tumor activity in the current study for MEDI4736 among bevacizumab naive or bevacizumab resistant, recurrent glioblastoma subjects, would provide a justification for randomized, definitive clinical trials of MEDI4736 for these subjects.

2.1 Rationale for Amendment 2

Per Protocol Amendment 2, two additional cohorts will be added to the study. The 2 additional cohorts will have the same study population criteria as Cohort B, which is defined as subjects with refractory GBM (first or second recurrence) who have not previously been treated with bevacizumab. The treatments for the 2 additional cohorts will be as follows:

- **Cohort B2** - MEDI4736 (10 mg/kg Q2W) + bevacizumab (10 mg/kg Q2W) on the same treatment days for 13 four-week cycles
- **Cohort B3 -** MEDI4736 (10 mg/kg Q2W) + bevacizumab (3 mg/kg Q2W) on the same treatment days for 13 four-week cycles

The hypothesis is that the anti-tumor activity of MEDI4736 will be enhanced when administered with bevacizumab among recurrent GBM subjects. Furthermore, we anticipate that the combination of MEDI4736 plus bevacizumab will be well tolerated among recurrent GBM subjects because the toxicity profiles of MEDI4736 and bevacizumab do not overlap indicating that these two agents are expected to be well tolerated when co-administered. In addition, per Protocol Amendment 2, dosing for Cohort B2 will be the same as that of Cohort C (MEDI4736 10

mg/kg Q2W + bevacizumab 10 mg/kg Q2W). At this time, 5 of the 6 subjects in the safety run-in for Cohort C have completed the DLT observation period without experiencing a DLT.

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is currently approved in the US and Australia for recurrent GBM. Despite durable radiographic responses, bevacizumab fails to improve overall survival.(3, 83, 84, 86) Growing data suggest that VEGF inhibition may enhance the anti-tumor benefit of immunotherapies by several potential mechanisms. First, VEGF is known to significantly contribute to the immunosuppressive microenvironment of tumors.(87-89) Specifically, VEGF can inhibit dendritic cell (DC) maturation and antigen presentation, induce apoptosis of CD8+ T cells, enhance Treg activity and diminish infiltration of T cells across tumor endothelium.(90-93) Second, preclinical studies demonstrate that immunotherapeutics may be combined with VEGF inhibitors to generate enhanced anti-tumor benefit.(88-99) Specifically, VEGF blockade can decrease tumor immunosuppression(90-93, 97-99) and enhance the anti-tumor activity of co-administered immunotherapies.(94, 96-99) Third, preclinical strategies to normalize tumor vasculature, including administration of anti-VEGF therapy, can shift tumor-associated macrophages from an M2 immune-inhibitory phenotype to an immune-stimulatory M1-phenotype, as well as increase tumor infiltrating CD8+ T cells and enhance survival following whole tumor cell vaccination.(95) Fourth, VEGF has been shown to induce FasL expression by tumor endothelial cells which selectively kills effector CD8+ T cells but not Tregs; VEGF blockade can thereby lead to increased influx of tumor-rejecting CD8+ over FoxP3+ T cells.(100) With regard to clinical application, limited data from studies evaluating anti-VEGF therapy plus immune checkpoint blockade have been published, but results from a recent Phase 1 study among subjects with metastatic melanoma reveal that administration of bevacizumab with ipilimumab, an inhibitor of the CTLA-4 immune checkpoint, led to improved overall survival as well as increased immune cell trafficking into tumor sites.(80)

In addition to the potential immune-enhancing features of anti-VEGF therapy, another important benefit is that co-administration of bevacizumab leads to decreased dexamethasone requirement for subjects with GBM.(3, 83, 101) Dexamethasone is routinely administered to treat symptomatic cerebral edema among GBM patients; however, systemic corticosteroid use has been shown to diminish the anti-tumor benefit associated with immune checkpoint blockade among patients with brain melanoma metastases.(102)

According to Amendment 2, the study will evaluate MEDI4736 combined with bevacizumab administered using either a standard (10 mg/kg biweekly; Cohort B2) or a reduced (3 mg/kg biweekly; Cohort B3) dosing schedule. Although the hypothesis is that VEGF blockade will enhance the anti-tumor activity of anti-PD-1/PD-L1 therapy, a currently unanswered critical question is whether there is an optimized dosing schedule of bevacizumab to do so. Standard bevacizumab dosing, administered as single agent therapy, represents the approved schedule for recurrent GBM based on durable radiographic responses.(75) In fact, as a monotherapeutic, a higher dosing schedule of bevacizumab may be required to achieve a sufficient anti-angiogenic effect to translate into anti-tumor benefit. However, higher (standard) dosing has also been shown to significantly decrease perfusion and tumor vasculature permeability, leading to intratumoral hypoxia which may in turn drive GBM invasion and infiltration.(103-107) In contrast, a lower dosing schedule has been shown to normalize rather than eradicate tumor vasculature, leading to improved blood flow, less hypoxia and enhanced delivery of co-administered anti-tumor agents in preclinical cancer models including GBM.(108, 109)

Normalized vasculature has also been associated with enhanced survival among cancer patients including those with GBM treated with anti-VEGF therapy.(110, 111) Furthermore, additional preclinical studies demonstrate that normalized tumor vasculature following reduced anti-VEGF therapy also leads to enhanced intratumoral immune cell infiltration.(95, 112) Finally, a recently published preclinical study evaluating lower versus higher doses of anti-VEGF therapy showed that only lower anti-VEGF therapy dosing led to enhanced immune infiltrate and improved survival following co-administration with an anti-tumor immunotherapeutic.(95)

A prospective evaluation of standard versus reduced bevacizumab dosing has not been conducted for subjects with GBM. A retrospective review of 219 subjects treated with bevacizumab showed that subjects treated with lower dose intensity (< 5 mg/kg per week) of bevacizumab had longer PFS and OS when compared with those treated with the standard 10 mg/kg biweekly dosing. (113)

3 Experimental Plan

3.1 Study Design

3.1.1 Study Phase

Phase 2

3.1.2 Enrollment/Randomization

Subjects will be enrolled in parallel and independently in all cohorts in a non-randomized, sequential manner, with competitive enrollment between study sites. Enrollment will be under ongoing review by an internal data safety monitoring panel (see Section 3.1.14, Safety Monitoring and Study Stopping Rules). For each cohort, the first study drug administration for the first subject and the second subject will be separated by at least 1 week (see Section 3.1.7, Treatment Arms and Treatment Schema). Eligible subjects have to be registered centrally with the Sponsor before enrollment.

Per Protocol Amendment 2, two cohorts (B2 and B3) will be added to the study as described in Section 2.1. Subjects in Cohorts B2 and B3 will be enrolled in a concurrent randomized manner.

3.1.3 Blinding/Unblinding

Open label.

3.1.4 Subject Population

Cohort A: Subjects with newly diagnosed unmethylated MGMT glioblastoma scheduled for standard radiotherapy.

Cohorts B, B2 and B3: Bevacizumab-naïve subjects with recurrent glioblastoma.

Cohort C: Bevacizumab-refractory subjects with recurrent glioblastoma.

For complete Subject Eligibility details, see Section 5.

3.1.5 Number of Sites/Subjects

Up to 172 subjects in 7 sites will participate as follows:

Cohort A: 37 subjects, including the first 6 subjects who will be evaluated for DLTs to confirm the suitability of the MEDI4736 dose in combination with standard radiotherapy. Up to 12 additional subjects may be required if the dose needs to be reduced (see Section 3.1.6.1).

Cohort B: 30 subjects

Cohort B2: 32 subjects

Cohort B3: 32 subjects

Cohort C: 17 subjects, including the first 6 subjects who will be evaluated for DLTs to confirm the suitability of the MEDI4736 dose in combination with bevacizumab. Up to 12 additional subjects may be required if the dose needs to be reduced (see Section 3.1.6.3).

Additional subjects may be enrolled in accordance with the subject replacement criteria in Section 3.1.11.

3.1.6 Sample Size Considerations

3.1.6.1 Cohort A

Overall survival at 12 months of newly diagnosed unmethylated MGMT GBM subjects treated with standard radiotherapy is 50%, based on the Phase 3 EORTC 26981-22981/NCIC CE3 study.(1) As discussed in Section 1.4, the addition of temozolomide in this subject population provides negligible survival benefit at the expense of increased toxicities.

An increase of the overall survival rate at 12-months from 50% to 70% is considered clinically relevant and justifies further investigation of MEDI4736 in this subject population. With 80% power and 0.05 significance level, using a one-sided exact binomial, to test a null hypothesis of 50% in historical controls against a one-sided alternative of 70% requires 24 of 37 subjects to be alive at 12 months.

The DLT evaluation of the first 6 subjects to confirm the suitability of the initial 10 mg/kg RP2D follows the principles of standard 3+3 dose escalation studies, i.e., if ≤1 of 3 subjects develops DLT, expand to 6, and if >1 of 3 or >1 of 6 subjects develop DLT, de-escalate to the next lower dose level. If at any of the three defined dose levels (10, 3, or 1 mg/kg) ≤1 of 6 subjects develops DLT, this dose level will be expanded to the full 37 subjects sample size. This process may require up to 18 subjects, of which 6 will be part of the expanded cohort. If at the lowest dose level >1 subject develops DLT, this cohort will be discontinued.

3.1.6.2 Cohort B

Three large meta-analyses of clinical trials performed among recurrent glioblastoma subjects in the modern, pre-bevacizumab era, reveal that only 10% of subjects remain progression-free for six months (PFS-6) or longer with salvage therapy.(114-116) The current study will therefore incorporate a PFS-6 of 10% as the comparative historical benchmark. If the true PFS-6 rate on the current study were 30% or higher, there would be interest in further investigation of this treatment regimen, and if the PFS-6 rate were ≤ 10%, there would be limited interest. Therefore, the study will be used to differentiate between a 10% and 30% rate of PFS-6, testing the hypothesis H_0: $p \leq 0.1$ versus H_1: $p \geq 0.3$, with p being the proportion of subjects remaining progression free for at least six months. Enrollment of 30 subjects will yield 80% power to detect a 20% difference in PFS-6 at an alpha level of 0.05 (one-sided). If at least seven subjects achieve PFS-6, the null hypothesis will be rejected in favor of the alternative hypothesis.

3.1.6.2.1 Cohorts B2 and B3

Outcome for subjects enrolled in Cohorts B2 or B3 will be separately compared to established historical benchmarks of bevacizumab for recurrent GBM. Among 85 subjects with GBM at first or second recurrence, PFS-6 was 42.6% (97.5 CI, 29.6% to 55.5%) following bevacizumab monotherapy in the BRAIN study.(3) This result coupled with an objective response rate of 28% was the basis for accelerated approval of bevacizumab for recurrent GBM patients in the United States.(75) In a recently reported Phase 2 study (BELOB), PFS-6 was also 42% (95% CI, 29-55) for GBM subjects at first recurrence randomized to receive bevacizumab plus lomustine.(117) The current study will therefore incorporate a PFS-6 of 42% as the comparative historical benchmark

of bevacizumab for recurrent GBM subjects as achieved in the BRAIN and BELOB studies, respectively. If the true PFS-6 rate for Cohorts B2 or B3 for the current study were 62% or higher, there would be interest in further investigation of this treatment regimen, and if the PFS-6 rate were ≤ 42%, there would be limited interest. Therefore, the study will be used to differentiate between a 42% and 62% rate of PFS-6, testing the hypothesis H_0: p≤0.42 versus H_1: p≥0.62, with p being the proportion of subjects remaining progression free for at least six months. Enrollment of 32 subjects to each cohort will yield 80% power to detect a 20% difference in PFS-6 at an alpha level of 0.1 (one-sided). If at least 18 subjects per cohort achieve PFS-6, the null hypothesis will be rejected in favor of the alternative hypothesis for that cohort.

3.1.6.3 Cohort C

The outcome for recurrent GBM subjects who progress on bevacizumab and continue with further salvage therapy that includes bevacizumab is dismal. Quant (n=35), Torcuator (n=23), Reardon (n=23) and Lu-Emerson (n=14) reported median survivals of only 2.9 months, 3.3 months, 4.1 months and 2.8 months, respectively.(118-121) Thus, the rate of OS at 6 months for these subjects is expected to be approximately 25-35%, based on the broad experience established to date. Reardon et al reported that the median OS among subjects who received a second bevacizumab containing regimen after failing initial bevacizumab treatment was 5.9 months (95% CI: 4.4, 7.6) and the OS at 6 months was 49.2% (95% CI: 35.2, 61.8).(78) For the current study, if the true 6 month OS rate is 65% or higher, there will be interest in further investigation of this treatment regimen. However, if the OS-6 rate is ≤ 35%, there would be limited interest in pursuing the development of this treatment regimen in this subject population. Therefore, the study will be used to differentiate between a 35% and 65% rate of OS-6. Statistically, the hypothesis that will be tested is (p = proportion of subjects who are alive at 6 months): H0: p<0.35 versus H1: p>0.65 OS-6 for cohort C will be compared to the historical benchmark set by Reardon. Enrollment of 17 subjects will yield 90% power to detect an OS-6 rate of 65% at an alpha level of 0.1 (one-sided). If at least 9 subjects are alive by 6 months, the null hypothesis will be rejected in favor of the alternative hypothesis.

The DLT evaluation of the first 6 subjects to confirm the suitability of the 10 mg/kg RP2D of MEDI4736 combined with bevacizumab follows the principles of standard 3+3 dose escalation studies, i.e., if ≤1 of 3 subjects develops DLT, expand to 6, and if >1 of 3 or >1 of 6 subjects develop DLT, de-escalate to the next lower dose level. If at any of the three defined dose levels (10, 3, or 1 mg/kg) ≤1 of 6 subjects develops DLT, this dose level will be expanded to the full 17 subjects sample size. This process may require up to 18 subjects, of which 6 will be part of the expanded cohort. If at the lowest dose level >1 subject develops DLT, this cohort will be discontinued.

3.1.7 Treatment Arms and Treatment Schema

In all Cohorts, MEDI4736 will be administered intravenously in 0.9% sodium chloride or 5% (w/v) dextrose over 60 minutes (± 5 minutes) according to Section 6.1.4. Each subject will receive up to 26 administrations at 10 mg/kg body weight (or at a reduced dose level as specified below for Cohorts A and C) two weeks apart over 52 weeks as shown in Figure 1. Individual dosing adjustments per subject due to toxicity will be allowed, as described in Section 3.1.8.2. Subjects will be followed on study for 90 days after the last drug administration and off-study every 6 months for three years from the date of first dose of study treatment (see Section 3.1.16).

In Cohort A, treatment will start on Day 1 of the Standard Radiotherapy after maximum safe resection. Standard Radiotherapy is defined as focal radiotherapy administered at 2 Gy given daily 5 days per week for a total of 60 Gy over 30 fractions per local institutional guidelines or local prescribing information.

Cohort A will be started on MEDI4736 at 10 mg/kg body weight, which is the current RP2D based on previous Phase 1 monotherapy data. As there are no safety data available for this combination, the first 6 subjects will be observed in sequential groups of 3+3 for DLTs for a DLT evaluation period of 10 weeks (see DLT definitions in Section 3.1.9), and any necessary dose de-escalations to 3 mg/kg and 1 mg/kg will be made as follows:

- If ≤1 of the first 3 subjects develop DLT, 3 more subjects will be enrolled.
- If >1 of the first 3 subjects or >1 of the first 6 subjects develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 subjects enrolled at the next lower dose level.
- If at any of the 3 dose levels (10, 3, or 1 mg/kg) ≤1 of 6 subjects develop DLT, this dose level will be expanded to the full 37 subjects sample size.
- If at the lowest dose level >1 of the first 6 subjects develops DLT, Cohort A will be discontinued.

In Cohorts B, B2 and B3, the Day 1 treatment start must fall within 14 days of the last baseline magnetic resonance imaging (MRI) confirmation of first or second recurrence of GBM by diagnostic biopsy or contrast enhanced MRI per modified RANO criteria.(122)

No safety run-in will be performed for Cohort B as it uses MEDI4736 as monotherapy.

Per Protocol Amendment 2, Cohort B2 dosing will be the same as that of Cohort C (MEDI4736 10 mg/kg Q2W + bevacizumab 10 mg/kg Q2W). At this time, 5 of the 6 subjects in the safety run-in for Cohort C have completed the DLT observation period without experiencing a DLT; therefore, a safety run-in period for Cohort B2 will not be required. As Cohort B3 will have a lower dose bevacizumab along with the MEDI4736, a safety run-in period will not be required as well.

In Cohort C, the Day 1 treatment start must fall within 14 days of the last baseline MRI confirmation of first recurrence of GBM following initial bevacizumab therapy as defined by diagnostic biopsy or contrast enhanced MRI per modified RANO criteria.(122) Subjects will continue receiving bevacizumab at 10 mg/kg intravenous (IV) every 2 weeks. On each treatment day, MEDI4736 will be administered first followed by a one-hour observation period, after which, bevacizumab will be infused.

Cohort C will be started on MEDI4736 at 10 mg/kg body weight, which is the current RP2D based on previous Phase 1 monotherapy data. Since there is no safety data available for this combination, the first 6 subjects will be observed in groups of 3+3 for DLTs for a DLT evaluation period of 6 weeks (see DLT definitions in Section 3.1.9), and any necessary dose de-escalations to 3 mg/kg and 1 mg/kg will be made as follows:

- If ≤1 of the first 3 subjects develop DLT, 3 more subjects will be enrolled.
- If >1 of the first 3 subjects or >1 of the first 6 subjects develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 subjects enrolled at the next lower dose level.

- If at any of the 3 dose levels (10, 3, or 1 mg/kg) ≤1 of 6 subjects develop DLT, this dose level will be expanded to the full 17 subjects sample size.
- If at the lowest dose level >1 of the first 6 subjects develops DLT, Cohort C will be discontinued.

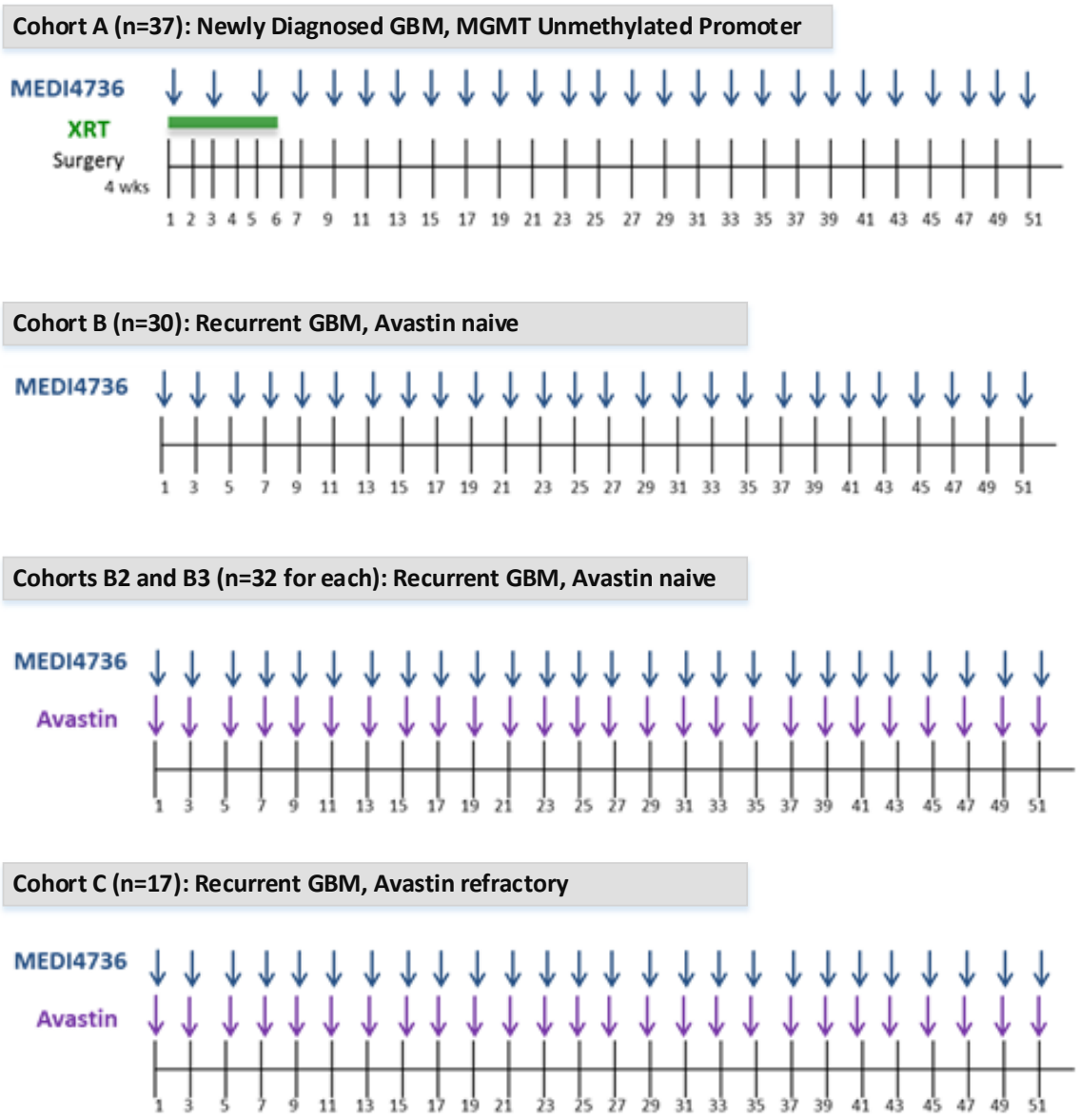

Figure 1

See Section 3.2, for complete treatment and assessment details for the cohorts.

3.1.8 Dosing Adjustments, Delays and Discontinuations

3.1.8.1 Radiotherapy (Cohort A only)

Dosing adjustment, delays and discontinuations of radiotherapy should be managed in accordance with institutional guidelines or local approved regulatory prescribing information.

3.1.8.2 MEDI4736 (Cohorts A, B, B2, B3 and C)

Dosing adjustment, delays and discontinuations for MEDI4736 should be managed in accordance with the instructions given in Appendix 8.6.

3.1.8.3 Bevacizumab (Cohorts B2, B3 and C)

Dosing delays and discontinuations of bevacizumab should be managed in accordance with institutional guidelines or local approved regulatory prescribing information.

3.1.9 DLT and MTD

DLTs will be observed over a DLT evaluation period of 10 weeks for Cohort A and 6 weeks for Cohort C; Cohorts B, B2, and B3 have no DLT evaluation period (see Section 3.1.11 for DLT evaluability). The decisions for dose de-escalations will primarily be based on the number of subjects with DLTs occurring during the DLT evaluation period. DLTs occurring outside the DLT evaluation period will also be evaluated and may impact such decisions.

DLTs are defined as any adverse events that are possibly, probably, or definitely related to the administration of MEDI4736 alone and/or the respective combination of MEDI4736 with radiotherapy or bevacizumab, and fulfill any of the following criteria:

1. Any Grade ≥ 3 colitis, pneumonitis, neurological event or uveitis.
2. Any Grade 2 pneumonitis, neurological event or uveitis with the *following exception*:
   - Grade 2 pneumonitis neurological event or uveitis that downgrades to Grade ≤ 1 within 3 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
3. Any *other* Grade ≥ 3 toxicity, with the *following exceptions*:
   - Grade 3 irAEs (see definition below) that downgrade to Grade ≤ 2 within 3 days, or to Grade ≤ 1 or baseline within 14 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
   - Grade 3 endocrinopathy that becomes asymptomatic when managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
   - Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
   - Grade 3 fatigue for ≤ 7days.
   - Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
   - Liver transaminase elevation ≤ 8 times the upper limit of normal (ULN) that downgrades to Grade ≤ 2 (≤ 5 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
   - Total bilirubin ≤ 5 times ULN that downgrades to Grade ≤ 2 (≤ 3 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
   - Grade ≥ 3 neutropenia that (1) is not associated with fever or systemic infection, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
   - Grade 3 or Grade 4 lymphopenia.

- Grade 3 thrombocytopenia that (1) is not associated with clinically significant bleeding, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
- Any pre-existing laboratory abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by both Investigator and Sponsor.

In Cohort A, if the planned radiotherapy dose cannot be reached or needs to be substantially interrupted (defined as either administration of less than 75% of planned XRT dose or XRT dosing is interrupted for more than two consecutive weeks) due to toxicity that is at least "possibly" related to the administration of MEDI4736, this should be counted as DLT.

In Cohort C, if the planned bevacizumab administration needs to be discontinued or substantially interrupted as per Prescribing Information due to toxicity that is at least "possibly" related to the administration of MEDI4736, this should be counted as DLT.

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

While rules for adjudicating DLTs are specified above, an AE that is Grade < 3 or listed as exempt above may also be defined as DLT after consultation with the Sponsor and Investigators, based on the emerging safety profiles of MEDI4736 alone and/or the respective combination of MEDI4736 with radiotherapy or bevacizumab. Likewise, subjects who become not evaluable for DLT, because they discontinued from the study or interrupted treatment due to toxicities other than DLTs, may be counted as DLT subjects, if the toxicities cannot be managed in accordance with the dosing modifications described in Section 3.1.8.

Subjects who experience a DLT will be discontinued from study therapy and will enter the On Study Follow-up period, followed by the Post Study Follow-up period (see Section 3.2). However, if it is in the best interest of the subject, the Investigator and Sponsor may agree to continue treatment, possibly at a lower dose level.

The MTD of MEDI4736 will not be determined in this study.

3.1.10 Subject Withdrawal from Treatment or from Study

A subject will be **withdrawn from study treatment** for any of the following reasons:

1. Withdrawal of consent for further treatment.
2. Pregnancy or intent to become pregnant.
3. Dose-limiting toxicity of MEDI4736 **at any time** (see Section 3.1.9 for definition of DLT and permitted continuation).
4. Confirmation of progressive disease by modified RANO criteria requiring alternative treatment.
5. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.

6. Development of intercurrent, non-cancer related illnesses or complications that prevent either continuation of therapy or regular follow-up.
7. Best medical interest of the subject (at the discretion of the Investigator)

A subject will be **withdrawn from the study** for the following reasons:

1. Best medical interest of the subject at the discretion of the Investigator.
2. Initiation of alternative anti-cancer therapy (marketed or investigational).
3. Withdrawal of consent for all follow-up.
4. Lost to follow-up.
5. Death

Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. If applicable, subjects who are withdrawn from study treatment should undergo the planned On Study Follow-up procedures (see Study Flowchart, Section 3.2), followed by the Post Study follow-up period (see Section 3.1.16).

Subjects who begin other anti-cancer therapy should immediately be considered as being off study and proceed to Post Study Follow-up.

NOTE: Subjects in Cohorts B2, B3, and C who are taken off treatment but continue bevacizumab alone should not be considered as having started new treatment. These subjects should continue into the On Study Follow-up visits, unless they are off study for other reasons.

General subject withdrawal criteria are outlined in the Administrative, Legal and Ethical Requirements section of the protocol (see Section 7.2.7).

See also Appendix 8.6 for subject withdrawal from treatment due to necessary dosing interruptions or discontinuations.

3.1.11 Subject Evaluability and Replacement

In Cohort A, subjects who are not fully evaluable per protocol for the primary objective of clinical efficacy per Section 4.1.2 may be replaced.

In the Safety Run-in portion of Cohort A, subjects who are not evaluable for DLTs during the DLT evaluation period as defined in Sections 3.1.7 and 3.1.9, will be replaced.

Subjects are evaluable for DLTs if:

a. they experienced a DLT as per Section 3.1.9, or
b. in the absence of a DLT, if they received at least 75% of the scheduled radiotherapy dose without dosing disruption for more than 2 consecutive weeks, and at least 4 of the 5 scheduled MEDI4736 doses over the first 8 weeks (Study Day 57), as well as, respective safety assessments, without major protocol violations, over the entire DLT evaluation period.

In Cohorts B, B2, and B3, subjects who are not fully evaluable per protocol for the primary objective of clinical efficacy per Section 4.1.2 may be replaced.

In Cohort C, subjects who are not fully evaluable per protocol for the primary objective of clinical efficacy per Section 4.1.2 may be replaced.

In the Safety Run-in portion of Cohort C, subjects who are not evaluable for DLTs during the DLT evaluation period, as defined in Sections 3.1.7 and 3.1.9, will replaced.

Subjects are evaluable for DLTs if:

(1) they experienced a DLT as per Section 3.1.9, or
(2) in the absence of a DLT, if they received at least 2 of the 3 scheduled bevacizumab doses and at least 2 of the 3 scheduled MEDI4736 doses over the first 4 weeks (Study Day 29), as well as, respective safety assessments, without major protocol violations, over the entire DLT evaluation period.

In all Cohorts, subjects who are being replaced may continue on study, unless another reason for discontinuation as defined in Section 3.1.10 occurs.

3.1.12 Optional Study Treatment Extension

Optional treatment extension beyond the 1-year study (Core Study) is available for subjects who complete 51 weeks of treatment on Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Appendix 8.8 for details.

3.1.13 Interim Analysis

Interim safety reviews will be performed to assess DLTs in context of the safety run-in for Cohorts A and C (see Section 3.1.7). Interim analyses may be performed to analyze the endpoints of progression free survival at 6 months and overall survival at 6 or 12 month for the applicable cohorts as specified in the statistical analysis plan.

3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal and Ethical Requirements section of the protocol (see Section 7), Safety Monitoring will be performed by an internal data safety monitoring panel, consisting of the Principal Investigators (and co-investigators as needed), the Sponsor Medical Monitor, and drug safety personnel from MedImmune, the provider of the study drug. Additional Investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews as indicated. An Independent Data Monitoring Board will not be utilized for this open label study.

The study will be suspended or possibly stopped prematurely for any of the following reasons:

1. A death that is unexpected and at least probably related to MEDI4736, or to the combination of radiotherapy or bevacizumab and MEDI4736.
2. Severe anaphylactic reaction to MEDI4736 (i.e., with respiratory and cardiovascular failure).
3. Any events that, in the judgment of the Medical Monitor, are at least probably related to MEDI4736 and are deemed serious enough to warrant immediate review by the internal data safety monitoring panel. This may include any symptomatic and/or

irreversible treatment-related grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related related grade ≥ 3 neurological toxicity or uveitis.

4. Any other safety finding assessed as related to MEDI4736 or its respective combinations with radiotherapy or bevacizumab that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
5. Any interim findings that, in the opinion of the Investigators and the Sponsor, suggest that the study treatment has no clinical benefit for the subjects.

Study stopping rules may be applied to individual cohorts, if the internal data safety monitoring panel concludes that the identified risk to one cohort does not carry over to another cohort.

General criteria for premature trial termination are outlined in the Administrative, Legal and Ethical Requirements section of the protocol (Section 7).

3.1.15 Duration of Study

Enrollment Period:	15 months
Duration of Treatment & Follow-up	15 months See Section 3.1.12 for optional treatment extension.
Length of Study:	27 months
Post Study Follow-up:	36 months

3.1.16 On Study and Post Study Follow-up

All subjects, whether they complete the study as planned, discontinue study treatment prematurely, or prematurely withdraw from the study as per Sections 3.1.10 and 7.2.7, will be followed as per institutional guidelines in accordance with the usual standard of care principles.

For all subjects who complete study treatment or discontinue treatment prematurely, there will be an On Study Follow-up for 90 days after the last MEDI4736 treatment, which will include collection of AE data (see Section 3.1.10 for subjects who begin other anti-cancer treatment and Section 7.1.5 for details on collection of AEs).

If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On-Study Follow-up Period (which is 14 days after the last dose of study treatment), any assessments required in the 14 day On Study Follow-up visit that are not covered as part of the last on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the last on-treatment visit and the 14 day On Study Follow-up visit should not be repeated.

Following the On Study Follow-up, there will be a Post Study Follow-up, where clinical outcomes data will be collected at least every 6 months for up to 3 years from the initiation of the treatment. Clinical outcomes data may include the following:

- First date of progression/relapse (for subjects who did not already progress while on study)
- First new anti-cancer treatment after the subject comes off study
- Survival data (including date/reason for death).

The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug.

For subjects who do not continue Post Study Follow-up at one of the study sites after the end of study, the Principal Investigators or the clinical team, under the supervision of the Principal Investigator, will obtain this data through review of outside records or communication with the subject or his/her physician.

See Section 3.1.12 for optional study treatment extension.

3.1.16.1 End of Study Visit

If a subject is **withdrawn from study** according to the criteria defined in Section 3.1.10, an End of Study visit must be conducted at the time of withdrawal. For subjects not yet in On Study Follow-up, this End of Study visit will be the first planned visit of the On Study Follow-up. For subjects already in On Study Follow-up, this End of Study visit will be the next planned visit of the On Study Follow-up. However, any procedures/assessments that were done within 7 days of the End of Study visit need not be repeated. All subjects of childbearing potential who withdraw from study must have a serum pregnancy test done at the End of Study visit unless it was done within 7 days prior to the End of Study Visit.

After the End of Study Visit, the subject will proceed into Post Study Follow-up as described above, unless otherwise unable to do so (e.g., subject withdraws consent for all follow-up).

3.2 Study Flowchart

Study Flowchart (1 of 3)	Screening / Baseline	Treatment									
Treatment weeks	**-4 to 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 9**	**Week 11**	**Week 13**
Treatment days	**-28 to 0**	**1**	**8±1**	**15±1**	**22±1**	**29±3**	**36±3**	**43±3**	**57±3**	**71±3**	**85±3**
Treatment (Cohort A)											
MEDI4736		x		x		x		x	x	x	x
Radiotherapy (Day 1-5) for 6 weeks		x	x	x	x	x	x				
Treatment (Cohort B)											
MEDI4736		x		x		x		x	x	x	x
Treatment (Cohort B2)											
MEDI4736		x		x		x		x	x	x	x
Bevacizumab (10mg/kg)		x		x		x		x	x	x	x
Treatment (Cohort B3)											
MEDI4736		x		x		x		x	x	x	x
Bevacizumab (3mg/kg)		x		x		x		x	x	x	x
Treatment (Cohort C)											
MEDI4736		x		x		x		x	x	x	x
Bevacizumab		x		x		x		x	x	x	x
Tumor & Disease Assessments											
Disease Staging (1st diagnosis & at study entry)	x										
Disease Assessment by modified RANO (including appropriate imaging)	x[5]								X		
Study Procedures & Examinations											
Eligibility Assessment[3,5]	x										
Demographics (incl. DoB; sex; height; race; ethnicity)	x										
Medical history and Pre-Existing Symptoms	x										
Physical Exam (incl. weight and ECOG Perf Status)	x	x		x		x			x		x
12-Lead ECG	x										
Vital Signs (T, HR, BP, RR). See Section 6.1.5 for assessment before/during/after MEDI4736 dose	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications and Procedures	-7 to 0	x	x	x	x	x	x	x	x	x	x
Adverse Events (starting or worsening after consent) [6]	x	x	x	x	x	x	x	x	x	x	x
Quality of Life (EORTC QLQ-C30/BN20)	x								x		
Neurologic Assessment in Neuro-Oncology (NANO)	x								x		
Laboratory Assessments											
Blood Hematology (CBC, differential, platelets)	-7 to 0	x[1]	x	x[1]	x	x[1]	x	x[1]	x[1]	x[1]	x[1]
Chemistry (gluc., BUN, creat., Na, K, Ca, Cl, CO_2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T_3, Free T_4, TSH)	-7 to 0	x[1]	x	x[1]	x	x[1]	x	x[1]	x[1]	x[1]	x[1]
Chemistry cont. (Amylase, lipase)	-7 to 0	x[1]	x	x[1]	x	x[1]	x	x[1]	x[1]	x[1]	x[1]
Urinalysis (Cohorts B2, B3, and C only)		x[2]		x[2]		x[2]		x[2]	x[2]	x[2]	x[2]
Serum pregnancy test (urine test only on Day 1)	-7 to 0	x[1]							x[1]		
MGMT expression (by standard, commercially available assay as per institutional guidelines)[7]	x										
IDH mutation (by standard, commercially available assay as per institutional guidelines)[7]	x										
Tumor Biopsy (PD-L1 expression)	x (archival)	x (at time of progression: optional)									
MDSC		x[4]				x[1]					
Flow Cytometry		x[4]	x	x[1]		x[1]			x[1]		
PBMC		x[4]	x	x[1]		x[1]					x[1]
Long-Term Follow-up											
Post Study Follow-up as described in Section 3.1.16											
1 - pre MEDI4736 dose on same day as infusion . Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing											
2 - pre bevacizumab dose; if urine protein dipstick is 2+ or greater, manage according to bevacizumab package insert											
3 - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart											
4- Samples may be collected up to 28 days prior to Day 1; if collected on Day 1, collection must be pre MEDI4736 dose.											
5 - For Cohorts B, B2, B3 and C, the last baseline MRI confirmation of first or second recurrence of GBM per modified RANO criteria must occur within 14 days of Day 1 of treatment.											
6 - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.											
7 - Archival results >28 days prior to the start of treatment are acceptable. If archival results are not available, this testing should be done within 28 days of start of treatment.											

Study Flowchart (2 of 3)	Treatment										
Treatment weeks	**Week 15**	**Week 17**	**Week 19**	**Week 21**	**Week 23**	**Week 25**	**Week 27**	**Week 29**	**Week 31**	**Week 33**	**Week 35**
Treatment days	**99±3**	**113±3**	**127±3**	**141±3**	**155±3**	**169±3**	**183±3**	**197±3**	**211±3**	**225±3**	**239±3**
Treatment (Cohort A)											
MEDI4736	x	x	x	x	x	x	x	x	x	x	x
Radiotherapy (Day 1-5) for 6 weeks											
Treatment (Cohort B)											
MEDI4736	x	x	x	x	x	x	x	x	x	x	x
Treatment (Cohort B2)											
MEDI4736	x	x	x	x	x	x	x	x	x	x	x
Bevacizumab (10mg/kg)	x	x	x	x	x	x	x	x	x	x	x
Treatment (Cohort B3)											
MEDI4736	x	x	x	x	x	x	x	x	x	x	x
Bevacizumab (3mg/kg)	x	x	x	x	x	x	x	x	x	x	x
Treatment (Cohort C)											
MEDI4736	x	x	x	x	x	x	x	x	x	x	x
Bevacizumab	x	x	x	x	x	x	x	x	x	x	x
Tumor & Disease Assessments											
Disease Staging (1st diagnosis & at study entry)											
Disease Assessment by modified RANO (including appropriate imaging)		X				X				X	
Study Procedures & Examinations											
Eligibility Assessment[3,5]											
Demographics (incl. DoB; sex; height; race; ethnicity)											
Medical history and Pre-Existing Symptoms											
Physical Exam (incl. weight and ECOG Perf Status)		x		x		x		x		x	
12-Lead ECG											
Vital Signs (T, HR, BP, RR). See Section 6.1.5 for assessment before/during/after MEDI4736 dose	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications and Procedures	x	x	x	x	x	x	x	x	x	x	x
Adverse Events (starting or worsening after consent) [6]	x	x	x	x	x	x	x	x	x	x	x
Quality of Life (EORTC QLQ-C30/BN20)		x				x				X	
Neurologic Assessment in Neuro-Oncology (NANO)		x				x				X	
Laboratory Assessments											
Blood Hematology (CBC, differential, platelets)	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1
Chemistry (gluc., BUN, creat., Na, K, Ca, Cl, CO_2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T_3, Free T_4, TSH)	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1
Chemistry cont. (Amylase, lipase)	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1
Urinalysis (Cohorts B2, B3, and C only)	x^2	x^2	x^2	x^2	x^2	x^2	x^2	x^2	x^2	x^2	x^2
Serum pregnancy test (urine test only on Day 1)		x^1				x^1				x^1	
MGMT expression (by standard, commercially available assay as per institutional guidelines)[7]											
IDH mutation (by standard, commercially available assay as per institutional guidelines)[7]											
Tumor Biopsy (PD-L1 expression)	x (at time of progression: optional)										
MDSC		x^1									
Flow Cytometry											
PBMC								x^1			
Long-Term Follow-up											
Post Study Follow-up as described in Section 3.1.16											

1 - pre MEDI4736 dose on same day as infusion. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing

2 - pre bevacizumab dose; if urine protein dipstick is 2+ or greater, manage according to bevacizumab package insert

3 - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart

4- Samples may be collected up to 28 days prior to Day 1; if collected on Day 1, collection must be pre MEDI4736 dose.

5 - For Cohorts B, B2, B3 and C, the last baseline MRI confirmation of first or second recurrence of GBM per modified RANO criteria must occur within 14 days of Day 1 of treatment.

6 - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

7 - Archival results >28 days prior to the start of treatment are acceptable. If archival results are not available, this testing should be done within 28 days of start of treatment.

Study Flowchart (3 of 3)	Treatment								On-Study Follow-up[6]			Post Study Follow-up (Done at least every 6 months for up to 3 years from start of treatment)
									Last Study Drug Admin +14 ± 3 days	Last Study Drug Admin +42 ± 5 days	Last Study Drug Admin +90 ± 7 days (End of Study)	
Treatment weeks	**Week 37**	**Week 39**	**Week 41**	**Week 43**	**Week 45**	**Week 47**	**Week 49**	**Week 51**	**Week 53**	**Week 57**	**Week 64 (End of Study)**	
Treatment days	**253±3**	**267±3**	**281±3**	**295±3**	**309±3**	**323±3**	**337±3**	**351±3**	**365±3**	**393±7**	**442±7**	
Treatment (Cohort A)												
MEDI4736	x	x	x	x	x	x	x	x				
Radiotherapy (Day 1-5) for 6 weeks												
Treatment (Cohort B)												
MEDI4736	x	x	x	x	x	x	x	x				
Treatment (Cohort B2)												
MEDI4736	x	x	x	x	x	x	x	x				
Bevacizumab (10mg/kg)	x	x	x	x	x	x	x	x				
Treatment (Cohort B3)												
MEDI4736	x	x	x	x	x	x	x	x				
Bevacizumab (3mg/kg)	x	x	x	x	x	x	x	x				
Treatment (Cohort C)												
MEDI4736	x	x	x	x	x	x	x	x				
Bevacizumab	x	x	x	x	x	x	x	x				
Tumor & Disease Assessments												
Disease Staging (1st diagnosis & at study entry)												
Disease Assessment by modified RANO (including appropriate imaging)			X				X		Every 8 weeks starting 8 weeks after last disease assessment			
Study Procedures & Examinations												
Eligibility Assessment[3,5]												
Demographics (incl. DoB; sex; height; race; ethnicity)												
Medical history and Pre-Existing Symptoms												
Physical Exam (incl. weight and ECOG Perf Status)	x		x		x		x		x	x	x	
12-Lead ECG												
Vital Signs (T, HR, BP, RR). See Section 6.1.5 for assessment before/during/after MEDI4736 dose	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications and Procedures	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events (starting or worsening after consent) [6]	x	x	x	x	x	x	x	x	x	x	x	
Quality of Life (EORTC QLQ-C30/BN20)			X				X					
Neurologic Assessment in Neuro-Oncology (NANO)			X				X					
Laboratory Assessments												
Blood Hematology (CBC, differential, platelets)	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x	x	x	
Chemistry (gluc., BUN, creat., Na, K, Ca, Cl, CO_2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T_3, Free T_4, TSH)	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x	x	x	
Chemistry cont. (Amylase, lipase)	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x^1	x	x	x	
Urinalysis (Cohorts B2, B3, and C only)	x^2	x^2	x^2	x^2	x^2	x^2	x^2	x^2				
Serum pregnancy test (urine test only on Day 1)			x^1				x^1		x		x	
MGMT expression (by standard, commercially available assay as per institutional guidelines)[7]												
IDH mutation (by standard, commercially available assay as per institutional guidelines)[7]												
Tumor Biopsy (PD-L1 expression)	x (at time of progression: optional)											
MDSC												
Flow Cytometry									x			
PBMC					x^1				x			
Long-Term Follow-up												
Post Study Follow-up as described in Section 3.1.16												x

1 - pre MEDI4736 dose on same day as infusion . Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing

2 - pre bevacizumab dose; if urine protein dipstick is 2+ or greater, manage according to bevacizumab package insert

3 - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart

4- Samples may be collected up to 28 days prior to Day 1; if collected on Day 1, collection must be pre MEDI4736 dose.

5 - For Cohorts B, B2, B3 and C, the last baseline MRI confirmation of first or second recurrence of GBM per modified RANO criteria must occur within 14 days of Day 1 of treatment.

6 - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

7 - Archival results >28 days prior to the start of treatment are acceptable. If archival results are not available, this testing should be done within 28 days of start of treatment.

4 Study Objectives & Endpoints

Primary Objectives	Evaluation of Clinical Efficacy. *Cohort A (newly diagnosed subjects with unmethylated MGMT GBM):* Primary Endpoint: Overall Survival (OS) Rate at 12 months. *Cohort B, B2, B3 (bevacizumab-naïve subjects with recurrent GBM):* Primary Endpoint: Progression-free survival rate at 6 months (PFS-6). *Cohort C (bevacizumab-refractory subjects with recurrent GBM):* Primary Endpoint: Overall Survival (OS) Rate at 6 months.
Secondary Objectives	*Cohorts A, B, B2, B3 and C:* 1. Evaluation of Safety and Tolerability. 2. Evaluation of Clinical Efficacy by median Progression-Free Survival, and Overall Survival as well as overall response rate (ORR). 3. Quality of Life (EORTC QLQ-30/BN20).
Exploratory Objectives	*Cohorts A, B, B2, B3 and C*: 1. Evaluation of subject neurologic function (NANO scale). 2. Evaluation of MEDI4736 biological activity.
Per Amendment 4, the collection of samples for MEDI4736 PK, ADA, sPD-L1, and circulating soluble factors was removed.	

4.1 Clinical Efficacy

The assessment of Clinical Efficacy is the primary objective of the study for all cohorts. However, the primary endpoints differ by cohort due to the difference in subject populations.

4.1.1 Endpoints and Assessment Methods

In Cohort A, the primary endpoint is the Overall Survival (OS) rate at 12 months.

In Cohorts B, B2 and B3, the primary endpoint is the percentage of subjects who remain progression free at 6 months (PFS-6)

In Cohort C, the primary endpoint is the Overall Survival (OS) rate at 6 months.

In all cohorts, secondary efficacy endpoints are a) median progression-free survival, b) median overall survival, and c) overall response rate (ORR).

4.1.1.1 Overall Survival (OS)

For Cohort A, Overall Survival (OS) will be measured for each subject with time origin at the time of diagnosis until recorded date of death or last follow-up. For Cohorts B, B2, B3, and C, OS will be measured for each subject with time origin at the date of Study Day 1 until recorded date of death or last follow-up. If a subject is still alive, they will be censored on the date of last follow-up. Every effort will be made to follow subjects for overall survival after they discontinue the study.

4.1.1.2 Overall Radiographic Response Rate (ORR)

Overall response rate (ORR) will be assessed by modified RANO criteria (122) (see Appendix 8.4). ORR is defined as the percentage of subjects meeting criteria of CR or PR over a period of at least 4 weeks. Every attempt should be made to use whichever imaging technique(s) and test(s) are used initially for repeat evaluations throughout the study. End of study tumor assessment will be at least 4 weeks from prior assessment, at the Investigator's discretion, and in accordance with the proposed modified RANO criteria.

Radiographic assessment of response will be performed as outlined in the Study Flowchart (Section 3.2) while subjects are receiving study therapy. Following completion of study therapy, radiographic assessment of response will continue at regular intervals for subjects who have not withdrawn from the study. Guidelines for ongoing response assessment for such subjects include MRI evaluation every 2 months during the first year after completing study therapy, every 3 months during the second year, every 4 months during the third year, and every six months thereafter. For subjects who achieve a radiographic response, follow-up imaging four weeks later is encouraged if feasible in order to confirm the response.

4.1.1.3 Progression-free Survival (PFS)

Progression-free survival will be defined as the number of days from the date of first dose to the date of earliest disease progression based on modified RANO criteria or to the date of death, if disease progression does not occur. All disease progression will be included regardless of whether the event occurred while subject was taking the study drug or had previously discontinued the study.

4.1.2 Subject Evaluation & Statistics

The analysis of the primary endpoint will be based on both the intent-to-treat (ITT) and the per-protocol (PP) populations. Subjects who received any dose of MEDI4736 and at least baseline and one post-baseline assessment will be included in the ITT population. Subjects who received at least 75% of the planned radiotherapy doses (Cohort A only), at least 75% of the planned bevacizumab doses (Cohort B2, B3 and C only), and at least 75% of the planned MEDI4736 doses, as well as, respective disease assessments, without major protocol violations, are considered fully evaluable and will be included in the PP population.

In each analysis population, the rate of Overall Survival for the primary endpoints will be calculated using the Kaplan-Meier method at month 12 for Cohort A subjects and month 6 for Cohort C subjects.

For Cohorts B, B2 and B3, the rate of progression-free survival at 6 months (PFS-6) will be calculated using a Kaplan-Meier Estimate and the corresponding 90% confidence intervals (CI). A one-sided binomial test will be used as a sensitivity analysis method to estimate PFS-6 and its 90% CIs.

Tumor Response as defined by the modified RANO criteria will be summarized and analyzed descriptively for each cohort among subjects with measurable disease at baseline. Ninety-five percent confidence intervals (95% CI) based on binomial distribution will be constructed for the estimated ORR.

The secondary endpoints of median PFS, and median OS will be calculated for the ITT population and PP population using the Kaplan-Meier method. In addition, survival curves will be generated on the basis of these estimates.

The analysis of PFS and OS will be updated based on data collected during the Post Study Follow-up (Section 3.1.16).

4.2 Safety and Tolerability

Assessment of overall safety and tolerability will be performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the Investigators.

4.2.1 Endpoints & Assessment Methods

Clinical laboratory tests, vital sign and weight measurements, physical exams, performance status evaluation, MRI scans and any other medically indicated assessments including subject interviews, will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. The Investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as adverse events. All "treatment-emergent" clinically significant abnormalities and deteriorations from time of signing of informed consent to the end of study visit should be recorded in the Case Report Forms as adverse events and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. See further adverse event documentation and reporting requirements in Section 7.1.

4.2.2 Subject Evaluation & Statistics

All subjects who receive any dose of MEDI4736 will be evaluated for safety and tolerability. Appropriate summaries of AEs, laboratory data and vital sign data will be presented. AEs will be listed individually per subject according to CTCAE version 4.03, and the number of subjects experiencing each AE will be summarized using descriptive statistics.

4.3 Health Related Quality of Life

4.3.1 Endpoints & Assessment Methods

Health related quality of life (HRQoL) will be self-reported and measured with the use of the validated core quality of life questionnaire (QLQ-C30) and a quality of life questionnaire specifically for subjects with brain tumors (BN-20) of the European Organization for Research and Treatment of Cancer (123-125) in each treatment cohort (see Appendix 8.5). The questionnaires can be completed by the subject or with the assistance of the examiner at baseline prior to initiation of study therapy, and then at study visits that include an MRI assessment while on study therapy (approximately every two months) according to the schedule in Section 3.2. The questionnaires should be completed prior to discussing treatment response at each specified visit whenever possible.

4.3.2 Subject Evaluation & Statistics

The evaluation of HRQoL will be measured by mean changes from baseline in the EORTC-QLQ-30 global health status/QoL composite scale and by mean changes from baseline in the remaining

EORTC QLQ-C30 and BN-20 scales. All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with 1) higher scores for a functional scale representing higher levels of functioning, 2) higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, 3) and higher scores for a symptom scale representing higher level of symptoms.

4.4 Neurologic Function

4.4.1 Endpoint and Assessment Method

Neurologic function of subjects in each treatment cohort will be assessed using The Neurologic Assessment in Neuro-Oncology (NANO) Scale: A Tool To Assess Neurologic Function for Integration in the Radiologic Assessment in Neuro-Oncology (RANO) Criteria (126) (see Appendix 8.5). The NANO scale is an objective and quantifiable metric of neurologic function that incorporates direct observation/testing of eight relevant neurologic domains designed to be evaluated quickly during a routine clinic visit. The NANO scale is designed to complement subjective, subject-reported outcomes such as health-related quality of life questionnaires. Level of function scores for each neurologic domain will be evaluated by a physician, physician assistant or nurse practitioner at baseline prior to initiation of study therapy, and then at study visits that include an MRI assessment while on study therapy (approximately every two months) according to the schedule in Section 3.2.

4.4.2 Subject Evaluation and Statistics

For this study, the NANO scale will not be used to define clinical progression. Changes in level of function scores for each neurologic domain defined by the NANO scale will be descriptively summarized on an individual subject basis over time. For each cohort, the median survival of subjects with and without significant neurologic decline as defined by the NANO scale (a ≥ 2 point decline in one or more neurologic domains attributable to underlying tumor and not due to co-morbid event or change in concurrent medication) will be estimated.

4.5 Biological activity of MEDI4736

Samples for exploratory pharmacodynamic assessments will be collected according to the schedule presented in Section 3.2.

4.5.1 Endpoints & Assessment Methods

Assessments may include but not be limited to:

- MEDI4736 PK and Anti-drug antibodies (ADA)
- Serum sPD-L1 levels
- Flow cytometry (immune monitoring)
- Peripheral blood mononuclear cells (PBMCs) will be collected and banked to potentially assess immune cell phenotypes and function as well as immune diversity.
- Levels of Circulating soluble factors (cytokine profiling)
- Levels of circulating myeloid derived suppressor cells (MDSC)
- PD-L1 tumor expression in archived tumor and fresh tumor, if available.

Per Amendment 4, the collection of samples for MEDI4736 PK, ADA, sPD-L1, and circulating soluble factors was removed.

4.5.2 Subject Evaluation & Statistics

Subjects who received at least one dose of MEDI4736, and provide baseline and at least one post-treatment sample (if applicable), will be evaluated. Results from these assessments will be evaluated in relation to outcome. Descriptive statistics will be used to summarize these measurements.

4.6 Exploratory Review and Analysis of Radiological Scans and Data

An exploratory review and analysis of radiological scans and other appropriate data will be conducted. See Appendix 8.7.9 for additional details.

4.7 Exploratory Analysis of Mutational Load

An exploratory analysis of mutational load will be conducted. See Appendix 8.7.10 for additional details.

5 Subject Eligibility

Note: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.

5.1 Inclusion Criteria

*Eligible subjects **must fulfill** all of the following criteria:*

Cohort A:	
1.	Subjects with newly diagnosed, untreated, unmethylated MGMT GBM who are eligible for standard radiation therapy;
Cohorts B, B2, B3 and C:	
2.	First or second recurrence of GBM by diagnostic biopsy or contrast enhanced MRI per modified RANO criteria (122), with last baseline MRI confirmation within 14 days prior to Study Day 1; [**NOTE**: Recurrence is defined as progression following therapy (i.e., chemotherapy; radiation). If the subject had a surgical resection for relapsed disease and no anti-tumor therapy was administered for up to 12 weeks, and the subject has further evidence of tumor growth or undergoes another resection, this will be considered as one episode of recurrence.]
3.	On Study Day 1, at least 12 weeks from prior radiotherapy (unless progressive disease outside of the radiation field or histopathologic confirmation of unequivocal tumor);
4.	Cohort B, B2, B3: No prior VEGF/VEGFR targeted therapy; Cohort C: No more than one prior bevacizumab regimen;
5.	Recovery from any prior treatment clinically significant, related adverse events to grade ≤ 1 or pretreatment baseline with the exception of alopecia and laboratory values listed per inclusion criteria;
Cohorts A, B, B2, B3 and C:	
6.	Subjects with measurable or non-measurable disease
7.	Histopathologic confirmation of glioblastoma;
8.	At the time of Study Day 1, subjects must be at least 4 weeks since major surgical procedure, open biopsy, or significant traumatic injury; there should be no anticipation of need for major surgical procedure during the course of the study. There should be no core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Study Day 1.
9.	Subjects who have previously been treated with the Optune™ device are eligible for the study as long as toxicity related to the treatment has resolved to ≤ Grade 1 or baseline
10.	ECOG ≤ 1 or Karnofsky performance status of ≥70;
11.	Adequate hematologic, renal and hepatic function, as defined below: • Absolute Neutrophil Count ≥ 1000/mm3 • Platelet count ≥ 100,000/mm3 • Total bilirubin ≤ 1.5 x ULN; or if subject has Gilbert syndrome, then total bilirubin ≤ 3 x ULN • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.0 x ULN • Creatinine ≤ 1.5x ULN or creatinine clearance (CrCl) ≥ 50 mL/min (using the Cockcroft-Gault formula):

	○ Female CrCl = (140 - age in years) x weight in kg x 0.85 /72 x serum creatinine in mg/dL ○ Male CrCl = (140 - age in years) x weight in kg x 1.00/72 x serum creatinine in mg/dL <u>Cohorts B2, B3 and C</u> • Urinary protein quantitative value of ≤ 30 mg/dL in urinalysis or ≤1+ on dipstick, unless quantitative protein is < 1000 mg in a 24 hour urine sample
12.	Age ≥ 18 years at date of consent
13.	Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act [HIPAA] in the USA) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations;

5.2 Exclusion Criteria

*Subjects **may not** enter the study if they fulfill any of the following criteria:*

All Cohorts	
1.	Primary tumors localized to the brainstem or spinal cord;
2.	Locally directed therapies including but not limited to stereotactic radiosurgery, re-irradiation, Gliadel, and therapeutics administered by direct injection or convection-enhanced delivery within 6 months of start of study treatment;
3.	Prior exposure to MEDI4736 or other anti-PD-1, anti-PD-L1, anti-CTLA4 antibodies;
4.	Presence of diffuse leptomeningeal disease or extracranial disease;
5.	Active, suspected or prior documented autoimmune disease (including inflammatory bowel disease, celiac disease, irritable bowel syndrome, Wegner's granulomatosis and Hashimoto's thyroiditis). Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll;
6.	Known primary immunodeficiency or active HIV;
7.	Known active or chronic viral hepatitis or history of any type of hepatitis within the last 6 months indicated by positive test for hepatitis B surface antigen (HBV sAG) or hepatitis C virus ribonucleic acid (HCV antibody);
8.	History of organ transplant requiring use of immunosuppressive medication;
9.	History of active tuberculosis;
10.	Significant active systemic illness including infections requiring intravenous antibiotics;
11.	Current pneumonitis or interstitial lung disease;
12.	Other invasive malignancy within 2 years prior to entry into the study, except for those treated with surgical therapy only;
13.	History of severe allergic reactions to any unknown allergens or any components of the study drugs;
14.	Any prior Grade ≥ 3 immune-related adverse event (irAE) or any prior corticosteroid-refractory irAE;
15.	Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study;
16.	Lack of availability for follow-up assessments;
17.	Lack of availability for Post Study Follow-up contacts to determine relapse and survival;
18.	Women who are breast-feeding or pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG);
19.	Women of childbearing potential not using a medically acceptable means of contraception for the duration of the study and unsterilized males not willing to abide by requirements for contraception as stated in Section 5.4;
20.	If a subject previously received another investigational treatment, the last dose of investigational treatment was administered within 4 weeks of Day 1 of the study;
21.	Any condition that, in the clinical judgment of the treating physician, is likely to prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.

22.	Cohorts B2, B3 and C: • Evidence of hemorrhage on the baseline MRI or CT scan other than those that are ≤ grade 1 and either post-operative or stable on at least two consecutive scans • Current use of warfarin sodium or any other Coumadin-derivative anticoagulant. Participant must be off Coumadin-derivative anticoagulants for at least seven days prior to starting study drug. Low molecular weight heparin and Factor Xa antagonists are allowed • History of clinically significant bleeding within 6 months of enrollment • History of arterial thromboembolism within 12 months prior to enrollment • Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 90 mmHg on antihypertensive medications) • Any prior history of hypertensive crisis or hypertensive encephalopathy • Clinically significant cardiovascular disease within 12 months prior to enrollment (or randomization), including myocardial infarction, unstable angina, grade 2 or greater peripheral vascular disease, cerebrovascular accident, transient ischemic attack, congestive heart failure, or arrhythmias not controlled by outpatient medication, percutaneous transluminal coronary angioplasty/stent • Evidence of bleeding diathesis or coagulopathy • History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment • Serious, non-healing wound, ulcer, or bone fracture
23.	Subjects must not donate blood while on study and for at least 90 days following the last MED4736 treatment.

5.3 Restrictions on Concomitant Therapies

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the study. Any concomitant medication(s), including herbal preparations taken during the study will be recorded.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care as described in Section 5.3.2, #8.

5.3.1 Non-Permitted Concomitant Therapies

*Subject **may not** receive the following concomitant therapies during the study:*

1.	Systemic treatment with high dose corticosteroids or other immunosuppressive treatments (e.g. dexamethasone > 4mg/day or bioequivalent for at least 3 days within 1 week of Study Day 1, methotrexate, chloroquine, azathioprine). See Section 5.3.2 for exceptions. Wash-out period: 4 weeks prior to Study Day 1 or as stated.
2.	Other cancer therapy (chemotherapy, radiation or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Study Day 1 (6 weeks for nitrosoureas).
3.	Live attenuated vaccines within 30 days before first and after last dose of MEDI4736.

5.3.2 Permitted Concomitant Therapies

*Subject **may** receive the following concomitant therapies during the study:*

1.	For subjects in Cohort C, bevacizumab may continue to be administered up to the start of study treatment if the subject is currently receiving it. A washout period for bevacizumab is not required.
2.	Systemic high dose (>4 mg/day) dexamethasone or bioequivalent corticosteroids to treat cerebral edema and for supportive postoperative management.
3.	Intranasal, inhaled or oral corticosteroids for treating mild to moderate asthma or allergies, or topical steroids for localized (< 5% of body surface area) dermatitis, not to exceed 10mg/day prednisone or bioequivalent corticosteroid.
4.	Physiologic replacement of glucocorticoids as maintenance therapy for adrenal insufficiency. Standard doses of hydrocortisone for maintenance therapy are up to 10–20 mg/m2/day divided 2–4 times per day. For a subject with a body surface area (BSA) of 1.73 m^2, this translates to a total dose of up to 34.6 mg of hydrocortisone per day. The equivalent dose of dexamethasone is up to 1.2 mg per day. Some subjects may additionally receive mineralocorticoid-replacement maintenance therapy with fludrocortisone. The maintenance dose of fludrocortisone for this indication is 0.05–0.1 mg/day.
5.	NSAIDs, acetylsalicylic acid and specific COX-2 inhibitors.
6.	Antihistamines and other non-steroidal anti-allergy medication.
7.	Hormone or hormone-related anti-cancer therapy.
8.	At the discretion of the Investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high dose corticosteroids to treat MEDI4736 related immune-mediated adverse reactions. Subjects should receive full supportive care, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is

	permitted however, caution should be exercised in subjects receiving bevacizumab (Cohorts B2, B3 and C) and additional International Normalized Ratio (INR) monitoring is recommended.
All prescription and nonprescription drugs must be recorded, listing generic (preferably) or brand name, indication, dose, route and dates of administration. All non-drug therapies must also be recorded.	

5.4 Special Requirements for Contraception

Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (see table below) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of MED4736. Non-sterilized male partners of a female subject must use male condoms plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Female subjects should also refrain from breastfeeding throughout the period described above.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Females will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use male condoms plus spermicide from screening through 90 days after last dose of MEDI4736. Female partners (of childbearing potential) of a male subject must use a highly effective method of contraception (see table below) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Male subjects should refrain from sperm donation throughout the period described above.

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

Acceptable highly effective methods of contraception are described in the following table:

Highly Effective[a] Methods of Contraception	
Barrier/Intrauterine Methods	**Hormonal Methods**
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[b]	• "Implants": Etonogestrel-releasing implants: e.g., Implanon® or Norplan® • "Intravaginal Devices": Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing® • "Injection": Medroxyprogesterone injection: e.g., Depo-Provera® • "Combined Pill": Normal and low dose combined oral contraceptive pill • "Patch": Norelgestromin / ethinylestradiol-releasing transdermal system: e.g., Ortho Evra® • "Minipill[c]": Progesterone based oral contraceptive pill using desogestrel: e.g., Cerazette®
[a] Highly effective (i.e. failure rate of <1% per year) [b] This is also considered a hormonal method [c] Cerazette® is currently the only highly effective progesterone based pill	

6 Study Drug Preparation and Administration

6.1 MEDI4736 (Durvalumab)

MEDI4736 is supplied by the Sponsor. Commercially available water for injection (WFI) and 0.9% (w/v) saline or 5% (w/v) dextrose will be supplied by each site. Please see Section 7.2.9, Study Drug Shipments & Accountability, for additional details.

6.1.1 Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	*Expiration/retest dates are documented on the Certificate of Analysis and/or stability certification or in the in the QA Disposition of Investigational Medicinal Product (IMP) Report.*		
Container Description	*Type:* Single use vial	*Material:*	*Size:*
Formulation	Lyophilized powder containing 200 mg MEDI4736. When reconstituted with 4 mL of WFI, the solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0.		
Active Ingredient Content	*Mass/Weight:* 200 mg	*Volume:* n/a	*Concentration:* n/a
Storage Conditions	+2°C to +8°C		
Stability after reconstitution	24h at 2 to 8°C and 4h at 25°C/ambient		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.1.2 Investigational Product Inspection

Each vial of MEDI4736 selected for dose preparation should be inspected. If there are any defects noted with the investigational product, the Investigator, Site Monitor, and Sponsor should be notified immediately.

6.1.3 Preparation

Preparation of MEDI4736 and preparation of the intravenous bag are to be performed aseptically by the IP Manager or designated personnel. No incompatibilities between MEDI4736 and polyvinylchloride or polyolefin copolymers have been observed.

MEDI4736 requires reconstitution prior to use. The reconstitution should be performed with 4 mL sterile WFI for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted MEDI4736 should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution

clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

Doses will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2 or 0.22 µm in-line filter. The volume of reconstituted MEDI4736 to add to the IV bag is calculated as follows:

Volume of MEDI4736 (mL)	=	Dose (mg/kg)	X	Subject Weight (kg)	÷	MEDI4736 Concentration (nominal 50 mg/mL)

A volume of 0.9% (w/v) saline or 5% (w/v) dextrose equal to the calculated volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to addition of MEDI4736. The calculated volume of MEDI4736 is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Example: For a subject weighing 80 kg and dosed at 10 mg/kg, 16 mL [10 mg/kg x 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose. First, 16.0 mL of diluent is removed from the IV bag, and then 16 mL of MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described below.

6.1.4 Administration

6.1.4.1 MEDI4736 Administration

The first day of dosing will be considered Day 1. Following preparation of the dose, the entire contents of the IV bag should be administered as an IV infusion over 60 (± 5) minutes, using a 0.2- or 0.22-µm in-line filter. **An infusion of less than 55 minutes is considered a deviation.**

After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used (unless prohibited by institutional practice). Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered. If the line was not flushed, documentation is required.

See Appendix 8.6.1.2 for details regarding infusion-related reactions.

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

A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product(s). Fully functional resuscitation facilities should be available.

Investigational product(s) must not be administered via IV push or bolus but as an IV infusion.

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

The total time between reconstitution of MEDI4736 to start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8 °C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. An infusion of less than 55 minutes is considered a deviation. However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.

MEDI4736 does not contain preservatives and any unused portion must be discarded.

MEDI4736 solution should not be infused with other solutions or medications.

The date, start time, interruption, and completion time of MEDI4736 administration must be recorded in the source documents.

Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.1.5.

6.1.4.2 Cohort A and Cohorts B2, B3 and C Administration

In Cohort A, focal radiotherapy will be administered at 2 Gy daily for a total of 60 Gy over 30 fractions per local institutional guidelines or local prescribing information. Treatment with MEDI4736 will start on Day 1 of radiotherapy. On days when radiotherapy and MEDI4736 overlap, radiotherapy will first be administered followed by MEDI4736. Subjects will be monitored during and after MEDI4736 infusion as indicated in Section 6.1.5.

In Cohorts B2, B3 and C, subjects will first be administered MEDI4736 and monitored according to Section 6.1.5. Following, the observation period, bevacizumab will be infused, according to prescribing information.

6.1.5 Monitoring of MEDI4736 Dose Administration

Subjects will be monitored before, during and after infusion with assessment of vital signs according to the table below:

Vital Signs Assessment on Study Drug Administration Days	Pre-dose	During Infusion	End of Infusion (± 5 minutes)	Post infusion + 30 minutes (± 5 minutes)	Post Infusion + 60 minutes (± 5minutes)
MEDI4736 Vital Signs	X	every 15 minutes (± 5 minutes)	X	X	x

If a subject tolerates treatment well for the first 4 doses of MEDI4736 (i.e., no infusion reactions), subsequent infusions in that subject can be monitored according to the following schedule. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

Vital Signs Assessment on Study Drug Administration Days (after week 8 [after first 4 doses])	Pre-dose	During Infusion	End of Infusion (± 5 minutes)	Post infusion + 15 minutes (± 5 minutes)
MEDI4736 Vital Signs	X	every 30 minutes (± 5 minutes)	X	X

6.2 Estimated Study Requirements

Drug	*Required Quantity*
MEDI4736	12500 vials
Additional MEDI4736 for optional study treatment extension per Section 3.1.12	2000 vials
Radiotherapy	Provided by the sites as standard of care
Bevacizumab	Provided by the sites as standard of care

6.3 Drug Overdose Management

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in this protocol by >10%. There are no known antidotes available for MEDI4736. Any overdoses with this drug should be managed symptomatically and reported, with or without associated AEs/SAEs, according to Sections 7.1.2.2, 7.1.5, and 7.1.6.

7 Administrative, Legal & Ethical Requirements

7.1 Documentation and Reporting of Adverse Events

7.1.1 Definitions

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

N.B.: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of LICR studies to include any events, intercurrent diseases and accidents observed while the subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods, under placebo or in a reference group receiving drug or non-drug therapy or no treatment.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening[A],
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly / birth defect or
6. Is another medically important condition[B].

A The term "life-threatening" in the definition of "serious" refers to an event in which the patient or subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

B Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient/subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

N.B.: The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/subject/event outcome or action criteria usually associated with events that pose a threat to patient's or subject's life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.2 Additional Expedited Reporting Requirements for this Study

For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (see Section 8.3 for Sponsor contact information) **and may result in submission of an SAE based on certain criteria outlined below**:

1. Pregnancy
2. Overdose (as defined in Section 6.3)
3. Hepatic Function Abnormality (as defined in Section 7.1.8).

7.1.2.1 Pregnancy

7.1.2.1.1 Maternal Exposure

Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of MEDI4736.

If a subject becomes pregnant during the course of the study, the study drugs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the drug 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 (see Section 7.1.6). 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 subject was discontinued from the study.

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

The Sponsor will work with the Investigator to ensure that all relevant information is provided 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.

7.1.2.1.2 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of MEDI4736.

Pregnancy of the subject'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 drug 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 subject'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.

7.1.2.2 Overdose

Any overdose (as defined in Section 6.3) of a study subject, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event** to the Sponsor. If the overdose results in an AE, the AE must also be recorded as an AE according to Section 7.1.5. 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 according to Section 7.1.6. There is currently no specific treatment in the event of an overdose of the study drugs. The Investigator will use clinical judgment to treat any overdose. See Section 6.3 for additional details.

7.1.2.3 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 7.1.8) 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, 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 MedImmune/AstraZeneca.

7.1.3 Severity of an Adverse Event

The severity of all serious and non-serious adverse events should be assessed according to the National Cancer Institute CTCAE Scale (Version 4.03).

7.1.4 Relationship of Adverse Events to Study Drug

The relationship of all serious and non-serious adverse events to the investigational agent(s) will be determined by the Investigator on the basis of their clinical judgment, using one of the following terms (in accordance with NCI Guideline "Expedited Adverse Event Reporting Requirements for NCI Investigational Agents", NCI Cancer Therapy Evaluation Program, January 2001):

Definitely related (The AE is *clearly related* to the investigational agent)
Probably related (The AE is *likely related* to the investigational agent)
Possibly related (The AE *may be related* to the investigational agent)
Unlikely related (The AE is *doubtfully related* to the investigational agent)
Unrelated (The AE is *clearly not related* to the investigational agent)

N.B.: When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal

relationship. Information provided in the IB and/or in the "Background" of this protocol may support these evaluations.

7.1.5 General Reporting Requirements

All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur:

a. from the date of signing the informed consent, and
b. until the off-study date or 90 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (See Section 3.1.10 for subjects who begin other anti-cancer treatment).

Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).

7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

In addition to the General Reporting Requirements specified in Section 7.1.5, all events meeting the criteria for an SAE as per Sections 7.1.1 and 7.1.2, irrespective of suspected causation, must be reported by the Investigator to the Sponsor's Drug Safety Contact (primarily) or, alternatively, to the Primary Sponsor Contact, within 24 hours of becoming aware of the event. This should be done using the "Initial Serious Adverse Event Report Form," provided by the Sponsor, or, if Medidata RAVE data capture is utilized, using the respective Adverse Event and Safety Case Summary eCRFs. This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. (Pregnancy, overdose, and hepatic function abnormality will be handled according to Section 7.1.2.) Note: If an SAE cannot be reported through the "Initial Serious Adverse Event Report Form" or through Medidata RAVE within 24 hours of becoming aware of the event, the Sponsor's Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, must be contacted by phone or email within 24 hours of becoming aware of the event. In this case, the phone or email notification can then be followed up by an "Initial Serious Adverse Event Report Form" or through Medidata RAVE within one working day of the event.

The expedited reports should be directed by fax or e-mail to the Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, as specified in "Sponsor Information," Appendix 8.3. Studies utilizing the Medidata "Safety Gateway", built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact.

In urgent cases, pre-notification via phone or informal e-mail should be considered.

Serious adverse events must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned a serious adverse event tracking number by the

Sponsor. Institutional Review Boards may have specific rules on which Adverse Events need to be reported expeditiously, as well as, the time frames for such reporting.

SAE Reports will be evaluated by the Sponsor's Medical Monitor. Regulatory authorities and other Investigators, as well as institutional and corporate partners, will be informed by the Sponsor as required by ICH guidelines, laws and regulations in the countries where the investigational agent is being administered. In particular, SAEs that are unexpected and for which a causal relationship with the study drug cannot be ruled out, will be reported by the Sponsor within 15 calendar days; if they are life-threatening or fatal, they will be reported within 7 Calendar days.

Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement.

7.1.7 Serious Adverse Event (SAE) Follow-up Requirements

Subjects experiencing SAEs should be followed closely until the condition resolves or stabilizes, and every effort should be made to clarify the underlying cause. Follow-up information related to SAEs must be submitted to the Sponsor as soon as relevant data are available, using the "SAE Follow-up Report Form", provided by the Sponsor, or, if Medidata RAVE data capture is utilized, using the respective Adverse Event and Safety Case Summary eCRFs.

7.1.8 Adverse Events of Special Interest (AESIs)

MEDI4736, as an anti-PD-L1 antibody that binds with high affinity and specificity to PD-L1 and blocks its binding to PD-1 and CD80, promotes anti-tumor immunity and tumor cell killing. Its potential risks are based on this mechanism of action and include immune-mediated reactions, such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neurotoxicity and pneumonitis. Immune checkpoint antibodies, such as anti-PD-1 or anti-CTLA-4, can have a wide spectrum of immune-mediated reactions of inflammatory nature and can affect any organ of the body.

An AESI is an event of scientific and medical interest specific to understanding of the investigational product(s) and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid recording of all AEs including AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the investigational product(s).

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 aetiology. 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 AE being an irAE, the Investigator should promptly contact the Medical Monitor.

If an AESI also meets SAE criteria, the event will be reported as an SAE per Section 7.1.6.

AESIs observed with MEDI4736 and those considered AESIs for the purpose of this study are listed below. Further information on these AESIs (e.g. presenting symptoms) can be found in the current version of the MEDI4736 Investigator's Brochure. Guidelines for the management of subjects experiencing these toxicities can be found in Appendices 8.6 and 8.6.1 and in the following Medimmune guideline: ***"Medimmune's Dosing Modification and Toxicity Management Guidelines for Immune- mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."***

- **Colitis**
  Diarrhea and colitis are the most commonly observed treatment-emergent AEs following dosing with MEDI4736. In rare cases colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome, if not properly managed.
- **Pneumonitis**
  Adverse events of pneumonitis have been observed with anti-PD-1, and anti-PD-L1antibodies.(6) (48) Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Typically, pulmonary consultation is required.
- **Hepatic Function Abnormality (Hepatotoxicty, Hepatitis)**
  Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies.(6) 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 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a concurrent or pre-existing disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Cases where a subject shows an AST **or** ALT ≥ 3 x ULN **or** total bilirubin ≥ 2 x 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.
- **Neurotoxicity (Neuropathy/Neuromuscular toxicity)**
  Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.

- **Endocrine Disorders**
  Immune-mediated endocrinopathies include hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus
  Type 1 diabetes mellitus: For subjects with suspected diabetes mellitus, Investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin.

- **Dermatitis**
  Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.

- **Nephritis**
  Consult with Nephrologist should be done as well as monitoring 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.). Subjects 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.

- **Pancreatic Disorders**
  Immune-mediated pancreatitis includes autoimmune pancreatitis (or labs suggestive of pancreatitis); increased serum lipase, increased serum amylase).

- **Infusion Reactions**
  Adverse events of infusion reactions (also termed infusion-related reactions) are defined as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time.

- **Hypersensitivity Reactions**
  Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy.(6) As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies (MAbs) can be caused by various mechanisms, including acute anaphylactic (IgE-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.

7.2 Administrative Sponsor Requirements

7.2.1 Pre-Study Requirements

The following is required before study drug can be shipped to the study site:

- Satisfactory Site Validation (conducted by Sponsor, if applicable)
- Signed Statement of Investigator
- Regulatory Approval (e.g., active IND or equivalent)

- Institutional Review Board approval of Protocol and Informed Consent Form
- Executed Clinical Trial Agreement (if applicable)

7.2.2 Study Master Files

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system ("Study Master File") of all trial-related documentation that is suitable for inspection by the Sponsor and regulatory authorities. Upon completion of the trial, the Investigator is required to submit a summary report to the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by the Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

7.2.3 Case Report Form Data Collection

Electronic Case Report Forms (eCRF) will be completed in accordance with respective guidance and after training provided by the Sponsor. The use of eCRFs encompasses electronic data entry, query management and sign-off. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines (whichever provides the greatest protection to the integrity of the data).

All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.

The Investigator will sign and date the completed eCRF sections. This signature will indicate a thorough inspection of the data in the CRF and will certify its content.

7.2.4 Language

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. Case Report Forms must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the trial site.

7.2.5 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site validation, site initiation, routine monitoring and site close-out. Clinical Monitors and/or other Sponsor staff will meet with the Investigator staff and require direct access to source data/documents. Such access may also be required for Institutional Review Board review, and regulatory inspection/audits. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and Sponsor's proprietary information will be exercised.

It is the Clinical Monitor's responsibility to inspect the case report forms at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and

consistency of the data, and adherence to Good Clinical Practice guidelines. The Clinical Monitor should have access to subject charts, laboratory reports and other subject records needed to verify the entries on the case report forms ("source data verification").

7.2.6 Protocol Amendments

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Institutional Review Board and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals. However, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments that do not affect the safety of the subjects do usually not require prior Institutional Review Board approval, just notification.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

7.2.7 Premature Subject Withdrawal

A subject may withdraw from treatment or from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw subjects from treatment or from the study. Specific subject withdrawal criteria are listed in Section 3.1.10. Should a subject (or a subject's legally authorized representative) decide to withdraw, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

A complete final evaluation should be made at the time of the subject's withdrawal from treatment or from study. The appropriate section in the case report form should be completed with an explanation of why the subject is withdrawing, and an attempt should be made to perform a follow-up evaluation.

7.2.8 Early Trial Termination

Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14. In such case, one party must notify the other in advance in writing about the intent of and the reasons for the termination. The Investigator must also notify the appropriate Institutional Review Board accordingly.

7.2.9 Study Drug Shipments & Accountability

Study drug shipments will be addressed to the Principal Investigator's authorized designee, preferably, the site's pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt to the shipper.

A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- the subject's identification (subject number and code)
- date and quantity of drug dispensed
- date and quantity of drug returned to the Investigator/pharmacy (if applicable)

- date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the Clinical Monitor. The Investigator is responsible for seeing to it that all used and unused trial supplies are accounted for. At the end of the study, the Clinical Monitor will also collect the original study drug dispensing records.

At the end of the study or as directed by the Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by the Sponsor, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed-off by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

7.3 Regulatory, Legal & Ethical Requirements

7.3.1 Good Clinical Practice (GCP), Laws and Regulations

The Investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

7.3.2 Informed Consent

The Investigator must obtain witnessed (if applicable) written informed consent from the subject or the subject's legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study procedures are performed. The subject should be given a copy of the informed consent documentation. The original signed and dated informed consent form must be retained in the study records at the study site, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

7.3.3 Institutional Review Board

The Investigator must obtain written approval from the appropriate Institutional Review Board for the protocol and informed consent, and all amendments thereof, prior to recruitment of subjects and prior to shipment of investigational agents.

The Investigator must report Serious Adverse Events (SAEs) to the appropriate Institutional Review Board in accordance with the Institutional Review Board's rules and guidelines (see also Section 7.1).

The Investigator must assure that continuing review (at least once per year) of the study is performed by the Institutional Review Board throughout the duration of the study. If so required by the Institutional Review Board, the Investigator must provide study reports on an annual basis and upon completion of the study.

All correspondence with, and reports to, the Institutional Review Board must be maintained in the study files at the study site and copies must be sent to the Sponsor.

7.3.4 Subject Confidentiality

The Investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their initials, date of birth and subject number on the case report forms or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential section of the study file by the Investigator.

The Investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the subject's medical record that is directly related to the study. As part of the informed consent process, the subject must have given written consent that his/her records will be reviewed in this manner.

7.3.5 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. The expected distribution of men and women enrolled is based on the experience with other clinical trials at the study sites included in this study. The anticipated study population will be about 50% male and 50% female.

8 Appendices

8.1 Protocol Version History

Version 000 (Original) **Issue Date: 23-July-2014** **Summary of Changes: Original Issue**
Version 001 (Amendment 1) **Issue Date: 02-April-2015** **Summary of Changes:** Based on updated information from MedImmune and to provide clarifications for the protocol, updates for this amendment are outlined below. Due to the extent of changes made in this amendment, a separate document (LUD2013-006 Amendment 1 Summary of Changes) was generated. The outline of changes is as follows: • Synopsis: The duration of the DLT evaluation period was corrected from 10 weeks to 6 weeks for Cohort C. • Section 2 (Study Rationale): Language was updated to clarify that subjects in Cohort A will not receive standard first line therapy of temozolomide + radiotherapy. • Section 3.1.5 (Number of Sites/Subjects): The number of subjects was changed from 96 to 108, and the number of sites was changed from 6 to 7. • Section 3.1.6.1 (Cohort A, Sample Size Considerations): In paragraph 2, the following sentence was changed (26 was changed to 24) "With 80% power and 0.05 significance level, using a one-sided exact binomial, to test a null hypothesis of 50% in historical controls against a one-sided alternative of 70% requires 24 of 37 subjects to be alive at 12 months." • Section 3.1.6.2 (Cohort B, Sample Size Considerations): In the next to last sentence, ORR was changed to PFS-6. • Section 3.1.6.3 (Cohort C, Sample Size Considerations): Additional background information and some wording corrections were added to provide support to the selection of the null hypothesis. A clear statement regarding the number of subjects necessary to be alive at 6 months in order to accept the alternative hypothesis was also added. • Section 3.1.7 (Treatment Arms and Treatment Schema): For Cohorts B and C, it was clarified that the last baseline MRI confirmation of first or second recurrence of GBM must occur within 14 days of Day 1 of treatment. Clarification was also provided to indicate that the Post Study Follow-up will continue for 3 years from initial treatment. • Section 3.1.9 (DLT and MTD): Additional DLT exclusions have been added, and the entire section was updated and restructured to be consistent with current MedImmune recommendations. Duration of DLT evaluation periods was added for the cohorts, and clarification of the DLT definition and permitted continuation was provided. • Section 3.1.10 (Subject Withdrawal): o Point 2 was clarified to indicate that subjects who experience DLTs of MEDI4736 at any time will be withdrawn from treatment and proceed to the On Study Follow-up period. o Death was added as a reason (#9) for withdrawal.

- The language has also been updated to clarify that subjects who are withdrawn from the study will proceed to the 90 day On Study Follow-up period, with the exception of subjects who start other anti-cancer therapy who should immediately proceed to Post Study Follow-up.

- Section 3.1.11 (Subject Evaluability and Replacement): The duration of the DLT evaluation periods for Cohorts A and C were deleted, and the DLT evaluability was clarified based on changes to Section 3.1.9.
- Section 3.1.14 (Safety Monitoring and Study Stopping Rules): Point 2 was changed to indicate that anaphylactic reaction refers to severe reactions such as those associated with respiratory and cardiovascular failure.
- Section 3.1.16 (Post Study Follow-up): Clarification was added to indicate that, for all subjects, there will be an On Study Follow-up for 90 days after the last MEDI4736 treatment, which will include collection of AE data. Following the On Study Follow-up, there will be a Post Study Follow-up.
- Section 3.2 (Study Flowchart):
  - The timing of Day 8 MEDI4736 PK and sPD-L1 samples for Cohort C was changed to single sampling only.
  - T3 and T4 have been clarified to indicate that Free T3 and Free T4 should be collected.
  - The Week 4 and Week 6 Physical exams and ECOG assessments have been moved to Week 3 and Week 5, respectively.
  - The End of Study Period was renamed as the On Study Follow-up. A footnote was added to indicate that during the On Study Follow-up, subjects who complete the study and those who discontinue treatment or are prematurely withdrawn from the study will be followed for 90 days post last day of treatment, and all AE s will be collected during the 90 day On Study Follow-up.
  - The flowchart was updated to clarify that there is a Post Study Follow-up schedule that is separate from the 90 day On Study Follow-up.
  - A footnote was added to indicate that, for Cohorts B and C, the last baseline MRI confirmation of first or second recurrence of GBM recurrence must occur within 14 days of Day 1 of treatment.
  - For the footnotes for pre dose samples, timeframes were added for the correlative samples (i.e., up to 15 minutes prior to start of infusion); for post infusion, a timeframe of up to +10 minutes was added.
- Section 4.1.1.1 (Overall Survival (OS): This section was modified to define OS as the time from original diagnosis to death or last follow-up for Cohort A. For Cohorts B and C, OS will be measured for each subject with time origin at the date of Study Day 1 until recorded date of death or last follow-up.
- Section 5.1 (Inclusion Criteria):
  - Inclusion criterion #2 was updated to clarify that, for Cohorts B and C, the last baseline MRI confirmation of first or second recurrence of GBM must occur within 14 days prior to Study Day 1.
  - The inclusion criterion originally numbered as #3 (“Patients with measurable or non-measurable disease,“ under the section for Cohorts B and C) was moved to the inclusion criteria for all cohorts and was re numbered as #6. Other criteria were re-numbered as appropriate.

- Inclusion criterion #10 was amended to more clearly indicate that subjects with Gilbert's syndrome have a higher threshold for elevated bilirubin.

- Section 5.2 (Exclusion Criteria): Exclusion criterion #2 was modified to exclude the listed therapies only if administered within the past 6 months prior to start of study treatment.
- Section 5.3.2 (Permitted Concomitant Therapies): A new item #1 has been added to clarify that subjects who are planning to enroll in Cohort C do NOT need to have a washout period for bevacizumab as this is a standard of care treatment and will be continued in combination with MEDI4736 on study. Other items were re-numbered as appropriate.
- Section 6.1.5 (Monitoring of MEDI4736 Dose Administration): The change indicates that a full 60 minutes of monitoring post end of MEDI4736 infusion may only be required for the first 4 doses of MEDI4736 treatment for a particular subject. If treatment is well tolerated for a particular subject, the post infusion observation period may be reduced to 15 minutes for the fifth dose, starting in Week 9. In addition, the observation frequency during the infusion may also be changed from every 15 minutes to every 30 minutes.
- Section 6.3 (Drug Overdose Management): Overdose was more specifically defined as administration in excess of that mandated by the protocol by >10%.
- Section 7.1.2 (Additional SAE Definitions for this Study): A new section was added as Section 7.1.2, Additional SAE Definitions for this Study: Pregnancy and Overdose. Other sections in Section 7.1 were renumbered as appropriate.
- Section 7.1.5 (General Reporting Requirements): This section was renumbered from 7.1.4 to 7.1.5 and language was clarified to indicate how AEs should be collected during the On Study Follow-up for subjects who have completed the study and for those who discontinue treatment or are withdrawn from the study.
- Section 7.1.6 (Expedited SAE Reporting Requirements): Additional detail was provided for SAE reporting requirements
- Section 7.1.7 (SAE Follow-up Requirements): Instructions were added to provide clarification if Medidata RAVE data capture is used.
- Section 7.1.8 (Adverse Events of Special Interest): The AESI descriptions have been moved from their original position in Appendix 8.6.2 and inserted as Section 7.1.8. The descriptions and definitions of the AESIs have also been updated according to MedImmune current information.
- Section 7.2.7 (Premature Subject Withdrawal): The second paragraph was changed to remove the specific name of the form to be used for recording subject withdrawal. In addition, the list of reasons for subject withdrawal was deleted as it is redundant with the list in Section 3.1.10.
- Appendix 8.1 (Protocol Version History): The format of the table was changed to allow more space for recording the Summary of Changes.
- Appendix 8.3 (Sponsor Information): The Clinical Project Manager was changed to [redacted]
- Appendix 8.4.1 (Evaluable for Objective Response): The Note section ("Participants who exhibit objective disease progression or die prior to the end of Cycle 1 will also be considered evaluable") was deleted.
- Appendix 8.4.4 (Response/Progression Categories): The Note for Complete Response and Partial Response was clarified to indicate that the content of the note applies to subjects

who have **only** non-measurable disease. The Progressive Disease criteria language was modified for greater clarity to indicate that any one of the listed criteria must be met.

- Appendix 8.4.6 (Study Continuation Beyond Initial Progressive Disease): The requirements under which subjects can continue treatment beyond initial progression have been modified to allow subjects to remain on study after confirmed objective progression as long as the subject continues to experience clinical benefit. The change was also made to the footnote in Appendix 8.4.6.1.
- Appendix 8.5: Health Related Quality of Life questionnaires were added to the protocol. Sections were re-numbered, as appropriate.
- Appendix 8.6 (MEDI4736 Toxicity Management and Dose Adjustments):
  - Two additional references (package inserts for nivolumab and pembrolizumab) were provided for the management of irAEs.
  - The sentence regarding continuation of dosing despite concurrent vitiligo and alopecia was deleted as it is included in the table in Appendix 8.6.1
  - The guideline from MedImmune for management of toxicity due to MEDI4736 was referenced in Appendix 8.6.
  - The table in Appendix 8.6.1 (Dose Modifications Due to Toxicity of MEDI4736) was modified and replaced with an updated table based on the most recent recommendations from MedImmune.
- Appendix 8.7.7.2 (Tumor Biopsies): The option to take samples from surgically resected tumors was added.
- Administrative changes:
  - The terms “patient(s)” and “participant(s)” were changed to “subject(s)” throughout the document, where appropriate (i.e., when referring to a study).
  - Study phase numbers were changed from Roman to Arabic numerals
  - General spelling and capitalization changes, as needed.

Amendment 2
Issue Date: 02-NOV-2015
Summary of Changes:

In order to add Cohorts B2 and B3 and to provide clarifications to the protocol, the following changes were made:

- Synopsis, Section 2.1: Modifications and rationale were provided for the addition of 2 cohorts. The additional cohorts will have the same study population criteria as Cohort B but will receive the following treatments:
  - Cohort B2 (n=32): MEDI4736 (10 mg/kg Q2W) + bevacizumab (10 mg/kg Q2W)
  - Cohort B3 (n=32): MEDI4736 (10 mg/kg Q2W) + bevacizumab (3 mg/kg Q2W)
- Section 3.1.2: The following was added: Subjects in Cohorts B2 and B3 will be enrolled in a concurrent randomized manner.
- Sections 3.1.4 and 3.1.5: Cohorts B2 and B3 were added and number of subjects in the study was updated.
- Section 3.1.6: section 3.1.6.2.1 was added for Cohorts B2 and B3 sample size consideration.

- Section 3.1.7: Cohorts B2 and B3 were added. The following was added: Per Protocol Amendment 2, Cohort B2 dosing will be the same as that of Cohort C (MEDI4736 10 mg/kg Q2W + bevacizumab 10 mg/kg Q2W). At this time, 5 of the 6 subjects in the safety run-in for Cohort C have completed the DLT observation period without experiencing a DLT; therefore, a safety run-in for Cohort B2 will not be required. As Cohort B3 will have a lower dose bevacizumab along with the MEDI4736, a safety run-in will not be required as well.
- Figure 1 was updated to include Cohorts B2 and B3
- Sections 3.1.8.2, 3.1.8.3, 3.1.9, and 3.1.11: Cohorts B2 and B3 were added as appropriate.
- Section 3.1.9:
    - neurological event and uveitis were added to #1, #2, and bullet for #2
    - For #3, bullet 2: "Grade 3 asymptomatic endocrinopathy" was changed to "Grade 3 endocrinopathy that becomes asymptomatic …"
- Section 3.1.10:
    - Section was clarified to indicate reasons for withdrawal from treatment vs. withdrawal from study.
    - Note was added to indicate that Subjects in Cohorts B2, B3, and C who are taken off treatment but continue bevacizumab alone should not be considered as having started new treatment. These subjects should continue into the On Study Follow-up visits.
- Section 3.1.15: enrollment period duration was updated.
- Section 3.1.16:
    - Clarification was provided for On Study Follow-up versus Post Study Follow-up.
    - Clarification was provided to indicate that If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On-Study Follow-up Period (which is 14 days after the last dose of study treatment), any assessments required in the 14 day post-last treatment visit that are not covered as part of the on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the protocol visit and 14 day post-last treatment visit should not be repeated.
- Section 3.2, Flowchart:
    - Added Cohorts B2 and B3 to study treatments and other assessments/footnotes as appropriate.
    - 12-lead ECG was added to the Screening Visit; previously omitted
    - Pregnancy test was added to the On Study Follow-up (Day +14 and Day +90 post last study drug); previously omitted.
    - Footnote 1 - Note was added indicating that blood chemistry, hematology, urinalysis and pregnancy test do NOT need to be done within 15 minutes prior to start of infusion as long as the sample is taken before the infusion and on the same day as the planned infusion)
    - Footnote 2 - Clarification was added to indicate if urine protein dipstick is 2+ or greater, manage according to bevacizumab package insert.
    - Footnote 6 - Clarification was added to indicate that During the On Study Follow-up, subjects who complete study treatment or discontinue treatment

prematurely (but are not withdrawn from study) will be followed for 90 days post last day of treatment; all AEs will be collected during this period. See Section 3.1.16 for details.
    - Footnote 7 was added indicating that the 28 day window for screening samples does not apply to MGMT and IDH testing; archival results are acceptable. If archival results are not available, this testing should be done within 28 days of start of treatment.
- Section 4: Cohorts B2 and B3 were added as appropriate
- Section 5.1 (Inclusion Criteria):
    - Added Cohorts B2 and B3 as appropriate
    - # 8 - updated language to read as follows: At the time of Study Day 1, subjects must be at least 4 weeks (changed from 3 weeks) since major surgical procedure, open biopsy, or significant traumatic injury; there should be no anticipation of need for major surgical procedure during the course of the study. There should be no core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Study Day 1.
    - #9: language was added to indicate: Subjects who have previously been treated with the Optune™ device are eligible for the study as long as toxicity related to the treatment has resolved to ≤ Grade 1 or baseline.
    - other inclusion criteria were re-numbered as appropriate
    - #11: The following was added for adequate renal function: Cohorts B2, B3 and C - Urinary protein quantitative value of ≤ 30 mg/dL in urinalysis or ≤1+ on dipstick, unless quantitative protein is < 1000 mg in a 24 hour urine sample.
- Section 5.2 (Exclusion Criteria):
    - #20 was clarified to indicate: If a subject previously received another investigational treatment, the last dose of investigational treatment was administered within 4 weeks of Day 1 of the study
    - #22 was added. The following exclusion criteria were added for Cohorts B2, B3, and C:
        - Evidence of hemorrhage on the baseline MRI or CT scan other than those that are ≤ grade 1 and either post-operative or stable on at least two consecutive scans
        - Current use of warfarin sodium or any other Coumadin-derivative anticoagulant. Participant must be off Coumadin-derivative anticoagulants for at least seven days prior to starting study drug. Low molecular weight heparin and Factor Xa antagonists are allowed
        - History of clinically significant bleeding within 6 months of enrollment
        - History of arterial thromboembolism within 12 months prior to enrollment
        - Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 90 mmHg on antihypertensive medications)
        - Any prior history of hypertensive crisis or hypertensive encephalopathy
        - Clinically significant cardiovascular disease within 12 months prior to enrollment (or randomization), including myocardial infarction, unstable angina, grade 2 or greater peripheral vascular disease,

cerebrovascular accident, transient ischemic attack, congestive heart failure, or arrhythmias not controlled by outpatient medication, percutaneous transluminal coronary angioplasty/stent
    - Evidence of bleeding diathesis or coagulopathy
    - History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment
    - Serious, non-healing wound, ulcer, or bone fracture
- Section 5.3.2: clarification was added to #8 to indicate that Use of anticoagulants such as warfarin is permitted; however, caution should be exercised in subjects receiving bevacizumab (Cohorts B2, B3 and C) and additional International Normalized Ratio (INR) monitoring is recommended.
- Section 6.1.4.2: Added Cohorts B2 and B3 to section describing order of administration for MEDI4736 and bevacizumab
- Section 6.2: updated drug requirements for MEDI4736
- Section 7.1.5: Clarification was provided for collection of AEs during the On Study Follow-up based on clarifications provided in Sections 3.1.10 and 3.1.16.
- Section 7.1.6: additional detail and clarification were added regarding reporting of SAEs to the Sponsor within 24 hours**.**
- Section 7.1.8: clarification was added regarding recording of AESIs. Expedited reporting by the Investigator to the Sponsor within 24 hours is not required
- Section 7.1.8.6, Uveitis, was added.
- Section 7.2.7: Section was updated to be aligned with Section 3.1.10.
- Appendix 8.3: Primary Sponsor Contact was changed from [redacted] to [redacted] who was already listed in this section as the Clinical Project Manager
- Appendix 8.6: all sections were updated based on the most recent dose modification guidelines from Medimmune
- Appendix 8.6.2: MEDI4736 Dose Modification Not Due to Toxicities was added
- Administrative Changes:
    - Updated formatting and logo in protocol to be consistent with new protocol format (SOP-C01 TMP 3 v3).
    - Spelling and grammar changes, as needed.

Amendment 3
Issue Date: 13-APR-2016
Summary of Changes:

- Synopsis: The following statement was added: "**Per Amendment 3**, optional treatment extension beyond the 1-year study (Core Study) is available for subjects who complete 51 weeks of treatment on Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Appendix 8.8 for details."
- Section 3.1.10:
    - Treatment withdrawal criterion #6 "Initiation of alternative anti-cancer therapy including another investigational agent" was moved to Study withdrawal criterion #2 and changed to "Initiation of alternative anti-cancer therapy (marketed or investigational)."

- The following phrase was removed form Study withdrawal criterion #1: "e.g., start of new treatment."

- Section 3.1.12 was updated to indicate that optional treatment extension beyond 1-year Core Study is permitted. The following statement was added: "Optional treatment extension beyond the 1-year study (Core Study) is available for subjects who complete 51 weeks of treatment on Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Appendix 8.8 for details.
- Section 3.1.13: section was updated to include the possibility of interim analyses; changes in bold. "~~**No formal interim analysis will be performed. Analyses**~~ **Interim safety reviews** will be performed to assess DLTs in context of the safety run-in for Cohorts A and C (see Section 3.1.7). **Interim analyses may be performed to analyze the endpoints of progression free survival at 6 months and overall survival at 6 or 12 month for the applicable cohorts as specified in the statistical analysis plan."**
- Section 3.1.15 and Section 3.1.16: reference was provided to Section 3.1.12 regarding optional study treatment extension.
- Section 3.1.16:
  - Paragraph 4 was changed **FROM**: "Following the On Study Follow-up, there will be a Post Study Follow-up, where clinical outcomes data (dates of progression/relapse and survival) will be collected at least every 6 months for up to 3 years from the initiation of the treatment." **TO**: "Following the On Study Follow-up, there will be a Post Study Follow-up, where clinical outcomes data will be collected at least every 6 months for up to 3 years from the initiation of the treatment. Clinical outcomes data may include the following:
    - First date of progression/relapse (for subjects who did not already progress while on study)
    - First new anti-cancer treatment after the subject comes off study
    - Survival data (including date/reason for death)."
  - The following statement was added: "The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug."
- Section 3.2, Study Flowchart:
  - Amylase and lipase assessments were added.
  - The following was added to the Vital Signs assessment line: "See Section 6.1.5 for assessment before/during/after MEDI4736 dose."
  - Footnote 1 was changed **FROM: "**pre MEDI4736 dose (15 to 0 min. Note: Blood chemistry, hematology, urinalysis and pregnancy test do NOT need to be done within 15 minutes prior to start of infusion as long as the sample is taken before the infusion and on the same day as the planned infusion)"
    TO: "pre MEDI4736 on same day as infusion."
  - Footnote 3 was changed **FROM: "**pre dose (-15 to 0 minutes) and post infusion (up to +10 minutes" **TO:** "pre MEDI4736 dose (on same day as infusion) and post MEDI4736 infusion (up to +10 minutes)."
  - Footnote 6 was changed: **FROM "**During the On Study Follow-up, subjects who complete study treatment or discontinue treatment prematurely (but are not withdrawn from study) will be followed for 90 days post last day of treatment; all AEs will be collected during this period. See Section 3.1.16 for details."

TO: "See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration."

- Footnote 8 was added: "Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
- Screening/baseline sample collections for circulating soluble factors, flow cytometry, and PBMC were deleted. MDSC collection was moved from baseline/screening visit to Day 1.
- Footnote 9 ("Samples may be collected up to 28 days prior to Day 1; if collected on Day 1, collection must be pre MEDI4736 dose.") was added for Day 1 collections of ADA, circulating soluble factors, MDSC, flow cytometry, and PBMC. This was done to allow sites to have flexibility for collecting the baseline samples.
- For Long-Term Follow-up: 2 lines were combined into one and changed to "Post Study Follow-up as described in Section 3.1.16."
- Blood volume collected at each visit was deleted, as this is provided in the Lab Manual.

- Section 4.1.2:
  - Paragraph 2: For Overall Survival (Cohorts A and C), one-sided Binomial test was changed to the Kaplan-Meier method.
  - Paragraph 3: For Cohorts B, B2, and B3, one-sided binomial test for PFS-6 was changed to: "Kaplan-Meier Estimate and the corresponding 90% confidence intervals (CI)." The following statement was added: "A one-sided binomial test will be used as a sensitivity analysis method to estimate PFS-6 and its 90% CIs."
- Section 5, Subject Eligibility: The following note was added: "Note: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
- Section 6.1, MEDI4736
  - Section 6.1.3, "Investigational Product Inspection," was moved to the position before "Preparation," and sections were re-numbered accordingly.
  - MEDI4736 Preparation and Administration sections were re-organized to remove redundancy and to improve clarity.
  - The following statements were added:
    - Each dose of investigational product should be administered using the following guidelines:
    - A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product(s). Fully functional resuscitation facilities should be available. Investigational product(s) must not be administered via IV push or bolus but as an IV infusion.
    - Investigational product(s) must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

- Infusion window was changed from ±10 minutes to ± 5 minutes, and the following statement was added: **"**An infusion of less than 55 minutes is considered a deviation." Infusion time window was also updated in Section 3.1.7.

- Section 6.2: Additional estimated MEDI4736 requirements (2000 vials) for optional study treatment extension was added.
- Section 7.1.5: language for reporting AEs was changed
  FROM: "Documentation of serious and non-serious adverse events includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. All serious and non-serious adverse events occurring between the date of signing the informed consent and the off-study date (which includes the 90 day On Study Follow-up period) must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. During the On Study Follow-up period, all AEs must be documented for 90 days after the last dose of study drug for subjects who complete the study as well as those subjects who discontinue study treatment prematurely (see Section 3.1.10 for subjects who begin other anti-cancer treatment)."
  TO: "All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur: a) from the date of signing the informed consent, and b) until the off-study date or 90 day after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment). Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).
- Section 7.2.3: the following statement was added: "All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF."
- Appendix 8.6: The statement, which referenced guidelines for ipilimumab, nivolumab, and pembrolizumab was deleted.
- Appendix 8.6.1 MEDI4736 Dose Modifications due to toxicity were updated according to current recommendations from MedImmune/AstraZeneca (Dated 02-OCT-2015).
- Appendix 8.6.2:
  - For Point 2, "7 days or less" was changed to "≤ half the planned dosing interval."
  - For Point 3, "7 days" was changed to "half the planned dosing interval."
- Appendix 8.8 was added to provide additional details and flowchart for subjects who continue treatment after the 1-year Core Study.
- Administrative:
  - Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

- Monitor and Study Monitor were standardized as “Clinical Monitor” in Sections 7.25 and 7.2.9.

Amendment 4
Issue Date: 31-OCT-2016
Summary of Changes:

- Synopsis and Sections 4.0, 4.5, 4.5.1, 8.7.1, 8.7.2, and 8.7.5: The following statement was added as appropriate: “**Per Amendment 4**, the collection of samples for MEDI4736 PK, ADA, sPD-L1, and circulating soluble factors was removed.”
- Synopsis and Section 4.0: MEDI4736 PK and immunogenicity were deleted from objectives, as appropriate.
- Section 3.1.16.1, End of Study Visit, was added.
- Section 3.2, Flowchart:
  - Deleted sampling for MED4736 PK, ADA, sPD-L1 and circulating soluble factors.
  - For Weeks 5 and 6, changed dosing window from ±1 to ±3 days
  - For Footnote 1, the following note was added: “Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.”
  - Deleted footnotes 3 and 4
  - Re-numbered footnotes 8 and 9 as footnotes 3 and 4, respectively.
  - Added ECOG Perf Status to Physical exam
  - Added Physical exam to On Study Follow-up visits
  - Changed Disease assessment during On Study Follow-up to be ”Every 8 weeks starting 8 weeks after last disease assessment”
- Sections 4.6 and 8.7.9, Exploratory Review and Analysis of Radiological Scans and Data, were added.
- Section 5.4, Special Requirements for Contraception: updated entire section for agreement with current Medimmune guidelines.
- Sections 6.0 and 8.8: dextrose was added as an optional diluent (in addition to saline) for MEDI4736.
- Section 6.1.4.1, MEDI4736 Administration:
  - The following statement was added: See Appendix 8.6.1.2 for details regarding infusion-related reactions.
  - The following change (in bold) was made): Investigational product(s) must be administered at room temperature by controlled infusion ~~**via an infusion pump**~~ into a peripheral vein or central line.
  - The following statement was changed **FROM: “**Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [w/v] Sodium Chloride for Injection), is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered.” **TO**: **“**MEDI4736 solution should not be infused with other solutions or medications.”
- Section 7.1.2, Additional SAE Definitions for this Study:
  - Section was renamed as Additional Expedited Reporting Requirements for this Study
  - Hepatic function abnormality was added to pregnancy and overdose

- Additional detail was added for each item according to updated Medimmune guidelines.

- Section 7.1.6, Expedited SAE Reporting:
  - The following sentence was changed **FROM**: "This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration, and pregnancy, or overdose as defined in Section 6.3." **TO:** "This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. (Pregnancy, overdose, and hepatic function abnormality will be handled according to Section 7.1.2.)"
  - The following statement was added: "Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement."
- Section 7.1.8, AESIs: additional details were added for AESIs to correspond with current Medimmune/AZ guidelines. Uveitis was deleted from the list, as it is not in the current recommendations.
- Appendix 8.6.1, MEDI4736 Toxicity Management Guidelines: Section was updated to correspond with current Medimmune/AZ guidelines (19August2016).
- Appendix 8.6.2, MEDI4736 Dose Modification Not Due to Treatment-related Toxicities: Section was changed

  FROM: MEDI4736 administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply: 1. If the subject misses 2 consecutive planned doses, the subject should be discontinued from treatment; 2. If the dosing interruption is ≤ half the planned dosing interval, the originally planned drug administration should be given. Any respective protocol deviation should be documented, if applicable; 3. If the dosing interruption is greater than half the planned dosing interval, the dosing should be skipped and the next scheduled drug administration should be performed. The respective protocol deviation should be documented.

  TO: MEDI4736 administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply: 1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 10 days. All resulting protocol deviations should be documented. NOTE: For subjects who continue treatment beyond the 1-year core study, the interval between any two doses shall be no less than 21 days.; 2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued; 3. If the dosing interruption is ≤ half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary; 4. If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary.
- Appendix 8.8.1, Preparation of Fixed Dose of 1500 mg for MEDI4736:
  - The following sentence was changed **FROM**: "Subjects will receive a fixed dose of MEDI4736, regardless of weight." **TO**: Subjects will receive a fixed dose of MEDI4736: 1500 mg Q4W for subjects > 30 kg. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will be dosed at 600 mg Q4W for MEDI4736 as long as the body weight remains ≤ 30 kg."

- Dextrose was added as an optional diluent for MEDI4736 (in addition to saline).
- Appendix 8.8.2, Appendix Flowchart:
  - Added ECOG Perf Status to Physical exam
  - Added Physical exam to On Study Follow-up visits
- Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

Amendment 5
Issue Date: 14-APR-2017
Summary of Changes:

1. Sections 4.7 and 8.7.10 (Exploratory Analysis of Mutational Load) were added to provide clarification of testing that is defined in the agreement with Dana Farber Cancer Institute.
2. Section 5.2, Exclusion Criteria: #23 was added; "Subjects must not donate blood while on study and for at least 90 days following the last MED4736 treatment."
3. Section 6.1.1 (Study Drug Information) and Sections 6.1.3 and 6.1.4 (Preparation and Administration of MEDI4736): Clarifications and additional details were provided based on current recommendations from Medimmune; added concentration of dextrose - 5% (w/v). Dextrose was also added to Section 3.1.7.For interruptions during infusion, total allowed time was changed from 4 to 8 hours
4. Section 7.1.8, AESIs: Additional detail was provided for the description of endocrine disorders (added Type 1 DM) and dermatitis.
5. Section 8.6.1.2 (Infusion related reactions): for Grades 1 and 2 : deleted "total infusion time not to exceed 4 hours"
6. Section 8.8 (Additional Details for Subjects who Continue treatment beyond core study): Clarificatiosn were provided to indicate that fixed dosing of 15000 mg Q4W if for subjects >30 kg
7. Section 8.8.1, Preparation of fixed dose of 1500 mg for MEDI4736:
   a. added concentration of dextrose - 5% (w/v).
   b. Paragraph 5 was changed to clarify that if a subject's weight drops to ≤ 30 kg, weight based dosing will be used (changes in bold): "Subjects will receive a fixed dose of MEDI4736: 1500 mg Q4W for subjects > 30 kg. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will **~~be dosed at 600 mg Q4W for MEDI4736 as long as the body weight remains ≤ 30 kg~~** **receive weight-based dosing equivalent to 20 mg/kg of MEDI4736 as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of MEDI4736 1500 mg.**

8.2 Participating Study Sites, Investigators, Staff and Laboratories

Study team roster will be maintained by the Sponsor.

8.3 Sponsor Information

Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 Tel: 212-450-1500	*Drug Safety Contact:* [redacted] Senior Manager, Drug Safety Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 [redacted] *Primary Sponsor Contact:* [redacted] Senior Clinical Project Manager Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 [redacted] *Clinical Monitoring:* [redacted] Clinical Research Associate The Ludwig Institute for Cancer Research 666 Third Avenue, 28th Floor New York, NY 10017 [redacted]

8.4 Tumor Response by Modified RANO

Tumor Response will be assessed by the by modified RANO criteria as outlined below and published by Wen et al.(122)

8.4.1 Evaluable for Objective Response

Only those subjects who have measurable disease as defined by modified RANO criteria (122) present at baseline (Cycle 1, Day 1 scan) and have received at least one dose of therapy will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

8.4.2 Measurable disease

Measurable disease is defined as bi-dimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. Enhancement around cysts or surgical cavities is in general considered non-measurable unless there is a nodular component measuring ≥ 10 mm in diameter. The cyst or surgical cavity should not be measured in determining response.

8.4.3 Non-measurable Evaluable Disease

Non-measurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameter < 1 cm.

8.4.4 Response/Progression Categories

Modified RANO criteria, as described below, will serve to define response classification for this protocol. As discussed in detail below, RANO criteria modifications to be used to assess response in this study address two relevant considerations for immune based therapies among GBM subjects including:
1) use of contrast enhancing changes to define progressive disease; and
2) allowance of specified subjects to continue study therapy following initial determination of progressive disease for up to 8 weeks in order to confirm progression.

Complete response (CR): All of the following criteria must be met:

a. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No new lesions.
c. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d. Subjects must be on no steroids or on physiologic replacement doses only.
e. Stable or improved non-enhancing (T2/FLAIR) lesions.
f. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related

NOTE: **Subjects with only non-measurable disease cannot have a complete response. The best response possible is stable disease.**

Partial response (PR): All of the following criteria must be met:

a. Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No progression of non-measurable disease.
c. No new lesions.
d. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e. The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
g. Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

NOTE: Subjects with only non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable disease (SD): All of the following criteria must be met:

a. Does not qualify for CR, PR, or progression.
b. All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c. Stable clinically.

Unknown response status

Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

Progressive disease (PD): Any one of the following criteria must be met:

a. 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids
b. Any new lesion
c. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the Investigator but may include a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, unless attributable to co-morbid events or changes in concurrently administered medications.
d. Failure to return for evaluation due to death or deteriorating condition.

8.4.5 Progressive Disease: Assessment Based on Contrast Enhancing Tumor Measurement

Immune based therapies are expected to be associated with inflammatory changes that may include edema. RANO expanded radiologic criteria to define progressive disease to include the development of "significantly" increased T2 or FLAIR abnormality because such changes can be a major component defining radiographic progression following therapeutic use of VEGF/VEGFR-targeting therapeutics which are known to elicit potent anti-permeability changes that limit contrast uptake. Our study will define radiographic progressive disease by assessment of enhancing tumor burden and will not incorporate assessment of T2 or FLAIR changes as outlined in RANO because:

1) there is no expectation that immunotherapy agents will falsely diminish enhancing tumor burden as has been noted with anti-angiogenic therapies; and
2) immune based therapies may be associated with increased edema and associated T2/FLAIR changes which may inaccurately be interpreted to represent tumor progression (i.e. pseudoprogression).

8.4.6 Study Continuation Beyond Initial Progressive Disease

Accumulating evidence indicates that some subjects treated with immunotherapeutics may develop apparent progression of disease (by conventional response criteria) before demonstrating objective responses and/or stable disease.(127) This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab, (48) a humanized monoclonal antibody against PD-1, and has also been reported for ipilimumab monotherapy.(127) In order to minimize premature discontinuation of study medication and distinguish pseudoprogression from progressive disease (PD), this protocol will include a modification of the standard RANO criteria for assessing GBM progression. The purpose of this modification is to permit continued study therapy at least until confirmation of PD. Specifically, subjects meeting criteria for progressive disease (Appendix 8.4.4) will be permitted to continue study medication at least until confirmation of progression with an MRI performed 8 weeks after suspected progression as long as the following criteria are met:

1) The subject is believed to demonstrate clinical benefit as determined by the treating physician;
2) The subject is tolerating study medication.

Assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

If progression is confirmed on follow-up imaging, defined as a 25% (±10%) increase from baseline or best response, then the date of disease progression will be the first date the subject met criteria for progression. Subjects who have confirmed disease progression will discontinue study medication if they are no longer experiencing clinical benefit and enter the follow-up/survival period of the study.

The modified RANO response criteria employed in this study to assess response are summarized in Appendix 8.4.6.1:

8.4.6.1 Modified RANO Response Criteria to Assess Response

	CR	PR	SD	PD[1]
T1+Gad	None	≥ 50% decrease	< 50% decrease but < 25% increase	≥ 25% increase
T2/FLAIR	Stable or decreased	Stable or decreased	Stable or decreased	NA
New lesion	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	NA
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Decreased
Requirement for Response	All	All	All	Any

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NA=not applicable (increase in corticosteroid dosing or increase in T2/FLAIR changes without clinical decline or increased enhancing tumor are not sufficient to define PD for this study).

[1]PD - Subjects who are benefiting from study therapy and tolerating it are permitted to continue study therapy following initial documentation of PD for at least up to 8 weeks in order to confirm underlying tumor progression (Appendix 8.4.4-8.4.6).

8.4.7 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before beginning of 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.

8.4.8 Evaluation of Best Response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI at least four weeks later, it will be recorded as a sustained response, lasting until the time of tumor progression. Subjects without measurable disease may only achieve SD or PD as their best "response."

8.5 Neurologic Function and Health Related Quality of Life Questionnaires

8.5.1 Neurologic Function in Neuro-Oncology (NANO) Scale

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms.

Domain Levels of Function
Please check 1 answer for each domain

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant

8.5.2 Health Related Quality of Life Questionnaire EORTC QLQ - C30

ENGLISH

EORTC QLQ - C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ___ ___ ___ ___

Your birthdate (Day, Month, Year): ___ ___ ___ ___ ___ ___ ___ ___

Today's date (Day, Month, Year): 31 ___ ___ ___ ___ ___ ___ ___ ___

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

8.5.3 Health Related Quality of Life Questionnaire EORTC QLQ - BN20

ENGLISH

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you feel uncertain about the future?	1	2	3	4
32. Did you feel you had setbacks in your condition?	1	2	3	4
33. Were you concerned about disruption of family life?	1	2	3	4
34. Did you have headaches?	1	2	3	4
35. Did your outlook on the future worsen?	1	2	3	4
36. Did you have double vision?	1	2	3	4
37. Was your vision blurred?	1	2	3	4
38. Did you have difficulty reading because of your vision?	1	2	3	4
39. Did you have seizures?	1	2	3	4
40. Did you have weakness on one side of your body?	1	2	3	4
41. Did you have trouble finding the right words to express yourself?	1	2	3	4
42. Did you have difficulty speaking?	1	2	3	4
43. Did you have trouble communicating your thoughts?	1	2	3	4
44. Did you feel drowsy during the daytime?	1	2	3	4
45. Did you have trouble with your coordination?	1	2	3	4
46. Did hair loss bother you?	1	2	3	4
47. Did itching of your skin bother you?	1	2	3	4
48. Did you have weakness of both legs?	1	2	3	4
49. Did you feel unsteady on your feet?	1	2	3	4
50. Did you have trouble controlling your bladder?	1	2	3	4

8.6 MEDI4736 Toxicity Management and Dose Adjustments

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 (irAE)s during the conduct of this study. IrAEs are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Potential irAEs may be similar to those seen with the use of ipilimumab and may include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies.(6, 48, 81, 128) Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-mediated etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy.

In general, the following are recommended:

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

MEDI4736 may be modified or discontinued as a result of toxicities as described in the table in Appendix 8.6.1. Dose modifications will not be required for AEs that are clearly not attributed to MEDI4736 (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

In addition, management guidelines for AEs of special interest (AESIs) are detailed in Section 7.1.8. All toxicities will be graded according to NCI CTCAE v4.03. In case of doubt, the Investigator should consult with the Medical Monitor.

Additional information and guidance regarding dose modification due to toxicity are provided from MedImmune in the following guideline:

"MedImmune's Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."

8.6.1 Dose Modifications Due to Toxicity of MEDI4736

Note: If MEDI4736 dosing is held temporarily until resolution of the event as per instructions below, treatment(s) should be skipped and resume at the next scheduled treatment date (and not at the date of resolution).

8.6.1.1 Immune-related Adverse Events (irAEs)

Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Maximum supportive care, including immunosuppressive medications, such as high dose steroids, is allowed to induce resolution of the event. **However, infliximab should not be used for management of immune-related hepatitis.**

In addition to the criteria for permanent discontinuation of MEDI4736 depicted below, **permanently discontinue MEDI4736 also for**:

- Any Grade rash with bullous skin formations.
- 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.

Management of irAEs may require administration of immunosuppressive medications (and/or hormone replacement therapy for endocrinopathies). Resolution of irAEs managed in this manner in the timeframes specified is acceptable.

Grade 1	• In general, no dose modification required. • For *pneumonitis/interstitial lung disease*, consider holding MEDI4736 dosing as clinically appropriate and during diagnostic work-up for other etiologies.
Grade 2	• In general, hold MEDI4736 until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue MEDI4736 permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of MEDI4736 may differ by event as detailed below. • For *pneumonitis/interstitial lung disease*, the decision to reinitiate MEDI4736 upon resolution shall be based upon treating physician's clinical judgment (as long as the event does not meet DLT criteria). • For *peripheral neuromotor syndromes*, such as *Guillain-Barre* and *Myasthenia Gravis*, follow general instructions above, but always discontinue MEDI4736 permanently if there are signs of respiratory insufficiency or autonomic instability. • For *endocrinopathies*, *other than isolated hypothyroidism*, follow general instructions above, but patients may be retreated if the endocrinopathy is controlled and the patient is clinically stable while requiring steroid doses of ≤ 10 mg/day prednisone equivalent. • For *isolated hypothyroidism* managed with hormone replacement therapy, and for *sensory neuropathy/neuropathic pain*, holding MEDI4736 is at the discretion of the Investigator. • For *elevated creatinine* or *rash*, MEDI4736 should be held until resolution to ≤ Grade 1 or baseline. • For *vitiligo*, no dose modification required.

Grade 3	• In general, hold MEDI4736 until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue MEDI4736 permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of MEDI4736 may differ by event as detailed below. • For *peripheral neuromotor syndromes (*such as *Guillain-Barre* and *Myasthenia Gravis),* apply respective Grade 2 rules. • For *endocrinopathies*, follow Grade 2 instructions above. • For *pneumonitis/interstitial lung disease, diarrhea/enterocolitis*, *and elevated serum creatinine (e.g., nephritis or renal dysfunction)* always discontinue MEDI4736 permanently. • For *asymptomatic increases of amylase or lipase* levels, hold MEDI4736, and if complete work up shows no evidence of pancreatitis, MEDi4736 may be continued • For *hepatitis*, discontinue MEDI4736 permanently for (1) transaminases or bilirubin not resolving to ≤ Grade 1 or baseline within 14 days, (2) transaminases > 8 × the upper limit of normal (ULN) or bilirubin > 5 × ULN, or (3) any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury"). • For *rash*, MEDI4736 should be held until resolution to ≤ Grade 1 or baseline.
Grade 4	• In general, discontinue MEDI4736 permanently. • For *endocrinopathies,* follow Grade 2 instructions above. • For *asymptomatic increases of amylase or lipase* levels, hold MEDI4736, and if complete work up shows no evidence of pancreatitis, MEDI4736 may be continued.

8.6.1.2 Infusion-related Reactions

Grade 1	• The infusion rate of MEDI4736 may be decreased 50% or temporarily interrupted until resolution of the event. • Acetaminophen and/or antihistamines may be administered per institutional standards at the discretion of the Investigator. • Premedication for subsequent doses should be considered. • Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions.
Grade 2	• Same as Grade 1, but consider giving subsequent infusions at 50% of the initial infusion rate.
Grade 3-4	• **The infusion must be stopped** immediately and treatment permanently discontinued. • Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

8.6.1.3 All other Adverse Events

Grade 1	• No dose modification required.
Grade 2	• Hold MEDI4736 until resolution to ≤ Grade 1 or baseline, and discontinue MEDI4736 permanently if such resolution does not occur within 60 days.
Grade 3	• Hold MEDI4736. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736 permanently
Grade 4	• In general, discontinue MEDI4736 permanently. • For isolated lab results, decision to discontinue should be based on accompanying clinical signs/symptoms and per Investigator's clinical judgment and in consultation with the Sponsor.

8.6.1.4 Cerebral Edema

Due to the immunologic nature of MEDI4736, cerebral edema could theoretically result as a consequence of MEDI4736 administration due to immune infiltration of the brain. Symptoms related to cerebral edema may include headache or neurologic deficit that is either new or worsened. Subjects with any signs or symptoms of cerebral edema should be treated as clinically appropriate including initiation or increased systemic corticosteroid dosing, treatment with an osmotic diuretic or surgical decompression. Subsequent MEDI4736 dosing should be immediately interrupted if significant clinical symptoms attributable to cerebral edema develop. Treatment with additional MEDI4736 doses may only be re-initiated if clinically significant symptoms attributable to cerebral edema have resolved to grade ≤ 1 or pre-treatment baseline. Subjects who develop CTCAE 4.0 grade 4 cerebral edema attributable to MEDI4736 administration should not receive any further MEDI4736 doses and should discontinue study therapy.

8.6.2 MEDI4736 Dose Modification Not Due to Treatment-related Toxicities

MEDI4736 administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply:

1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 10 days. All resulting protocol deviations should be documented. **NOTE:** For subjects who continue treatment beyond the 1-year Core study, the interval between any two doses shall be no less than 21 days.
2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
3. If the dosing interruption is ≤ half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary.
4. If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary.

8.7 Laboratory procedures

8.7.1 MEDI4736 Pharmacokinetics and Immunogenicity for Anti-drug antibodies (ADA)

Samples will be collected for analyses at time points designated in the study flowchart (Section 3.2).

A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the quantitative determination of MEDI4736 concentrations in serum.

Anti-MEDI4736 antibodies in human serum will be detected using a validated MSD electrochemiluminescence assay.

Per Amendment 4, the collection of samples for MEDI4736 PK and ADA was removed.

8.7.2 sPD-L1

Samples to assess serum sPD-L1 levels before and after treatment will be collected for analyses at time points designated in the study flowchart (Section 3.2). Its association with response to treatment and clinical outcome will be evaluated.

Per Amendment 4, the collection of samples for sPD-L1 was removed.

8.7.3 Flow Cytometry

Samples will be collected for analyses at time points designated in the study flowchart (Section 3.2)

Peripheral blood populations before and after treatment, including absolute lymphocyte counts, numbers of T cells, T-cell subsets, NK cells, and B cells as well as their cellular phenotypes will be assessed by flow cytometry to evaluate the association with treatment and subject responses.

8.7.4 PBMC Banking

Peripheral Blood Mononuclear Cells (PBMCs) will be isolated and banked as described below at time points designated in the study flowchart (Section 3.2)

These samples may be used to address several key questions:

- The diversity of the immune cell repertoire may be assessed in PBMCs based on VDJ coding region analysis to determine if clinical responses are correlated with immunodiversity and if repertoire changes occur in response to treatment.
- Functional assays such as ELISPOT or tetramer staining or intracellular cytokine analysis may be employed to assess the activation state or antigen specificity of immune cell populations in the periphery.
- Flow cytometric analyses to examine additional markers not included in the primary panel may be performed on banked samples to supplement our understanding of a subject's immune status.

8.7.5 Circulating soluble factors

Blood samples at baseline and following treatment with MEDI4736 will be collected for analyses of circulating levels of soluble factors such as cytokines and chemokines. They may include but are not limited to VEGF, FGF, TGF, IL-1 IL-2, IL-4, IL-6, IL-8, IL-10, IFN, G-CSF, TNF, and explore their association with treatment and clinical outcome.

Per Amendment 4, the collection of samples for circulating soluble factors was removed.

8.7.6 Myeloid derived suppressor cells (MDSC)

MDSCs constitute a heterogeneous population of immature myeloid cells with various immune suppressive functions including suppression of T-cell proliferation, inducement of T-cell apoptosis and disruption of T-cell signaling pathways. Levels of circulating MDSCs are increasingly recognized as important in determining clinical responses to novel drugs for cancer and autoimmune disease. Samples will be collected for analyses at time points designated in the study flowchart (Section 3.2).

MDSCs are defined as events that are:

$Lineage^{neg}$, $CD14^{pos}$, $HLA\text{--}DR^{low/neg}$

Each sample is analyzed using well-established flow cytometry techniques for the presence of MDSCs. For each sample a single data point will be delivered, being the mean of values for the percentage of Lineage ^{neg}, $CD14^{pos}$ events that are $HLA\text{--}DR^{low/neg}$ to study the effects of MEDI4736 therapy on levels of MDSCs in GBM subjects.

8.7.7 Archival Tumor Samples and Tumor Biopsies

8.7.7.1 Archival Tumor Samples

Archival tumor samples are required for all subjects. Formalin fixed paraffin embedded (FFPE) tumor samples will be collected for immunohistochemistry (IHC) and additional correlative markers (e.g., tumor mutation analysis, RNA analysis, and immunodiversity). If a tumor block cannot be provided for this study, then only freshly prepared unstained sections should be provided as described in the Laboratory Manual.

8.7.7.2 Tumor Biopsies

Tumor biopsy may be obtained during the study as an optional procedure according to Section 3.2.

Image-guided core needle tumor biopsy will be performed according to institutional practice. If clinically practical, at each time point, subjects will undergo 4 core biopsies, but a minimum of at least 3 core biopsies are required. The first and third core biopsies will be placed in formalin and processed for FFPE, while the second and fourth core biopsies (4th biopsy, if available) will be immediately frozen in liquid nitrogen or equivalent method and then stored at -60°C or below. In exceptional cases, excisional or punch biopsies are permitted and may be substituted for the required minimum of 3 core biopsies if sufficiently large (4 mm or greater in diameter).

Alternatively, equivalent samples can be taken from resected tumor in the case that a subject needs to have the tumor surgically removed at the time of progression as part of standard of care.

Tumor biopsies will be stored at MedImmune or an appropriate vendor selected by LICR. Core biopsies may be used for correlative studies such as IHC, tumor mutation analysis, RNA analysis, proteomic analysis, and immunodiversity. Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

8.7.8 Additional Translational and Exploratory Studies

Optional research studies may only be performed for subjects who voluntarily gave their consent for additional correlative research on the informed consent document. Subjects who declined consent to participate in additional translational studies will have their samples destroyed at the end of the study. Refusal to participate in this optional research will involve no penalty or loss of benefits to which the subject would otherwise be entitled. Based on the data generated during the study and/or in other studies, not all samples from subjects consenting to this optional research may be utilized.

8.7.9 Exploratory Review and Analysis of Radiological Scans and Data

This exploratory review and analysis of radiological scans and other appropriate data will be conducted to examine the time course and variability of imaging changes associated with treatment based on both conventional and advanced magnetic resonance imaging (MRI) sequences. The exploratory analysis will also examine the accuracy of available advanced imaging modalities acquired at the time of suspected tumor progression in predicting subsequent true progression as well as overall survival. This review and analysis will be confined to scans that were obtained from subjects while on study; scans obtained after subjects have completed the study are not part of the scope of this imaging analysis.

There are 2 objectives for the exploratory review and analysis:

- Objective 1: To determine the frequency, time of onset, and duration of pseudoprogression for subjects enrolled in the trial.
- Objective 2: To determine the diagnostic value of advanced imaging techniques for pseudoprogression.

In this study, the Investigator assessments will be used for efficacy analyses and subject treatment decisions. The exploratory review and analysis will not be used for efficacy determinations or to determine the correlation of these results with the efficacy evaluations as assessed by the study Investigators.

8.7.10 Exploratory Analysis of Mutational Load

Mutational load analysis using formalin-fixed, paraffin-embedded (FFPE) tissue samples for a subset of subjects will be conducted by Dana Farber Cancer Institute. The purpose of this study is to perform Whole Exome Sequencing (WES) on FFPE tissue slides derived from a subset of patients. The mutational pattern of FFPE-derived tumor DNA is revealed by comparison to matched normal DNA from peripheral blood. The study will be divided into 2 phases, a Pilot phase that also assesses the feasibility of the proposed experimental setup and subsequently a Small-Scale Study, which includes WES from FFPE-tissue and PBMCs from subjects.

8.8 Additional Details for Subjects who Continue Treatment after 1-Year Core Study

According to Section 3.1.12, optional treatment extension beyond 1-year Core Study is available for subjects who complete 51 weeks of treatment on Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator.

Optional treatment extension will continue according to the dosing defined for the respective subject in the Core Study, with the exception that MEDI4736 will be administered according to the currently recommended fixed dose of 1500 mg every 4 weeks (Q4W) for subjects > 30 kg, which is equivalent to 10 mg/kg Q2W or 20 mg/kg Q4W.

The following procedures will be implemented for subjects who continue study treatment beyond the Core Study:

1. Preparation of fixed dose of 1500 mg for MEDI4736 will be used; details are provided in Appendix 8.8.1.
2. The flowchart for optional treatment extension, which is provided in Appendix 8.8.2, will be followed.

For Cohorts B2, B3 and C, bevacizumab treatments may continue Q2W as defined for the Core Study. All data from the respective study visit (dosing, AEs, concomitant medications/procedures, lab results and urinalysis) should be recorded on the CRF.

8.8.1 Preparation of Fixed Dose of 1500 mg for MEDI4736

Each vial of MEDI4736 selected for dose preparation should be inspected. If there are any defects noted with the investigational product, the Investigator and Site Monitor Sponsor should be notified immediately.

Preparation of MEDI4736 and preparation of the intravenous bag are to be performed aseptically.

MEDI4736 requires reconstitution prior to use. Each vial contains 200 mg MEDI4736; after reconstitution, a 50 mg/mL solution is obtained.

The reconstitution should be performed with 4 mL sterile WFI for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted MEDI4736 should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

Subjects will receive a fixed dose of MEDI4736: 1500 mg Q4W for subjects > 30 kg. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of MEDI4736 as long as the body weight remains ≤ 30 kg (e.g., a 30 kg

subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of MEDI4736 1500 mg.

MEDI4736 will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose.

For a 1500 mg dose, 30 mL of reconstituted MEDI4736 is to be diluted in a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose. (NOTE: 8 vials, 32 mL, of reconstituted MEDI4736 are required in order to be able to measure 30 mL for the dilution.)

First, 30 mL of diluent is removed from the IV bag, and then 30 mL of MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Administration of MEDI4736 will proceed according to Section 6.1.4. Subjects will be monitored by assessment of vital signs before, during and after each MEDI4736 dose administration according to Section 6.1.5.

8.8.2 Study Flowchart for Subjects who Continue Study Treatment after 1-Year Core Study

Study Flowchart for Subjects who Continue Study Treatment after 1-Year Core Study	Optional Study Treatment Extension	On Study Follow-up[5]			Post Study Follow-up (Done at least every 6 months for up to 3 years from start of treatment)
		Last Study Drug Administration +28 (± 3) days	Last Study Drug Administration +56 (± 5) days	Last Study Drug Administration +91 (± 7) days	
Treatment (Cohorts A and B)					
MEDI4736 (1500 mg)	**Q4W** (±3days) starting on **Week 53**				
Treatment (Cohort B2)					
MEDI4736 (1500 mg)	**Q4W** (±3days) starting on **Week 53**				
Bevacizumab (10 mg/kg)[3]	**Q2W** (±3days) starting on **Week 53**				
Treatment (Cohort B3)					
MEDI4736 (1500 mg)	**Q4W** (±3days) starting on **Week 53**				
Bevacizumab (3 mg/kg)[3]	**Q2W** (±3days) starting on **Week 53**				
Treatment (Cohort C)					
MEDI4736 (1500 mg)	**Q4W** (±3days) starting on **Week 53**				
Bevacizumab (10 mg/kg)[3]	**Q2W** (±3days) starting on **Week 53**				
Tumor & Disease Assessments					
Disease Assessment by modified RANO (including appropriate imaging)	**SOC** starting on **Week 57**	**SOC**	**SOC**	**SOC**	
Study Procedures & Examinations					
Physical Exam (incl. weight and ECOG Perf Status)	**Q4W** (±3days) starting on **Week 53**	X	X	X	
Vital Signs (T, HR, BP, RR)[6]	**Q2W** (±3days) starting on **Week 53**	X	X	X	
Concomitant Medications and Procedures	**Q2W** (±3days) starting on **Week 53**	X	X	X	
Adverse Events (starting or worsening after consent)[5]	**Q2W** (±3days) starting on **Week 53**	X	X	X	
Quality of Life (EORTC QLQ-C30/BN20)	**Q8W** (±3days) starting on **Week 57**				
Neurologic Assessment in Neuro-Oncology (NANO)	**Q8W** (±3days) starting on **Week 57**				
Laboratory Assessments					
Blood Hematology (CBC, differential, platelets)[1]	**Q4W** (±3days) starting on **Week 53**	X	X	X	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO_2, prot., alb., bili., AST, ALT, LDH, ALP, Free T3, Free T4, TSH)[1]	**Q4W** (±3days) starting on **Week 53**	X	X	X	
Chemistry cont. (Amylase and lipase)[1]	**Q4W** (±3days) starting on **Week 53**	X	X	X	
Urinalysis (Cohorts B2, B3, and C only)[2,3]	**Q2W** (±3days) starting on **Week 53**				
Serum pregnancy test[1]	**Q8W** (±3days) starting on **Week 57**	X		X	
PBMC[1]	Week 53 (±3days)	x[4]			
Long-Term Follow-up					
Post Study Follow-up as described in Section 3.1.16					x
1 - pre administration of drug(s), if applicable - Note: hematology, chemistry and pregnancy test (when applicable) results must be available and reviewed before infusion.					
2 - pre bevacizumab dose; if urine protein dipstick is 2+ or greater, manage according to bevacizumab package insert					
3 - For Cohorts B2, B3 and C, bevacizumab treatments may continue every 2 weeks (Q2W) as defined for Year 1 Core Study. All data from the respective study visit (dosing, AEs, concomitant medications/procedures, lab results and urinalysis) should be recorded on the CRF.					
4 - Samples may be collected at the last study visit when the subject is discontinued from treatment.					
5 - See Section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.					
6 - See Section 6.1.5 for assessment of vital signs before, during and after MEDI4736 dose administration. Pre bevacizumab dose on days when no MEDI4736 dose is given					
Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SOC = Standard of Care.					

8.9 List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
APC	antigen presenting cell
AST	aspartate transaminase
AUC	area under the concentration time curve
BID	twice daily
CD	cluster of differentiation
CL	clearance
CL/F	apparent systemic clearance
Cmax	peak concentration
CNS	central nervous system
CRO	contract research organization
CT	computed tomography
CTC	circulating tumor cell
CTLA-4	cytotoxic T-lymphocyte antigen 4
DC	dendritic cell
DCR	disease control rate
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DoR	duration of response
DTIC	dacarbazine
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
FAAN	Food and Allergy Anaphylaxis Network
Fc	fragment crystallizable
GBM	glioblastoma
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Gy	Grey
HDPE	high density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
ILD	interstitial lung disease
INR	International Normalized Ratio
IRB	Institutional Review Board
irAE	immune-related adverse event
irRC	immune-related response criteria
IV	intravenous
IXRS	interactive voice/web response system
KA	keratoacanthoma
LVEF	left-ventricular-ejection-fraction
MAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MDSC	myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	methylguanine methyltransferase
miRNA	microRNA
mPFS	median progression-free survival
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition
NCIC	National Cancer Institute of Canada
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Disease
NSCLC	non-small cell lung cancer
OCT	ocular coherence tomography
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PPES	Palmar-Plantar Erythrodysesthaesia Syndrome
PRO	patient-reported outcome
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	once daily
QoL	quality of life
QTc	time between start of Q wave and end of T wave corrected for heart rate

RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
RPED	retinal pigment epithelial detachment
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
RVO	retinal vein occlusion
SAE	serious adverse event
SID	subject identification
sPD-L1	soluble programmed death ligand 1
SUSAR	suspected unexpected serious adverse reactions
tu	half-life
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
USA	United States of America
V	valine
Vc/F	Apparent volume of distribution
VDJ	variable, diverse, and joining gene segments
WFI	water for injection
WT	wild-type

9 References

1. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459-66.
2. Reardon DA, Perry JR, Brandes AA, Jalali R, Wick W. Advances in malignant glioma drug discovery. Expert Opin Drug Discov. 2011;6(7):739-53.
3. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(28):4733-40.
4. Kreisl TN, Zhang W, Odia Y, Shih JH, Butman JA, Hammoud D, et al. A phase II trial of single-agent bevacizumab in patients with recurrent anaplastic glioma. Neuro-oncology. 2011;13(10):1143-50.
5. Reardon DA, Turner S, Peters KB, Desjardins A, Gururangan S, Sampson JH, et al. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. Journal of the National Comprehensive Cancer Network : JNCCN. 2011;9(4):414-27.
6. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine. 2012;366(26):2455-65.
7. Weller M, Stupp R, Reifenberger G, Brandes AA, van den Bent MJ, Wick W, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nature reviews Neurology. 2010;6(1):39-51.
8. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. The New England journal of medicine. 2005;352(10):997-1003.
9. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J. 1992;11(11):3887-95.
10. Finger LR, Pu J, Wasserman R, Vibhakar R, Louie E, Hardy RR, et al. The human PD-1 gene: complete cDNA, genomic organization, and developmentally regulated expression in B cell progenitors. Gene. 1997;197(1-2):177-87.
11. Shinohara T, Taniwaki M, Ishida Y, Kawaichi M, Honjo T. Structure and chromosomal localization of the human PD-1 gene (PDCD1). Genomics. 1994;23(3):704-6.
12. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004;20(3):337-47.
13. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. The Journal of experimental medicine. 2000;192(7):1027-34.
14. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nature medicine. 1999;5(12):1365-9.
15. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature medicine. 2002;8(8):793-800.
16. Yamazaki T, Akiba H, Iwai H, Matsuda H, Aoki M, Tanno Y, et al. Expression of programmed death 1 ligands by murine T cells and APC. Journal of immunology. 2002;169(10):5538-45.

17. Yao Y, Tao R, Wang X, Wang Y, Mao Y, Zhou LF. B7-H1 is correlated with malignancy-grade gliomas but is not expressed exclusively on tumor stem-like cells. Neuro-oncology. 2009;11(6):757-66.
18. Wu C, Zhu Y, Jiang J, Zhao J, Zhang XG, Xu N. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. Acta histochemica. 2006;108(1):19-24.
19. Wintterle S, Schreiner B, Mitsdoerffer M, Schneider D, Chen L, Meyermann R, et al. Expression of the B7-related molecule B7-H1 by glioma cells: a potential mechanism of immune paralysis. Cancer research. 2003;63(21):7462-7.
20. Wilmotte R, Burkhardt K, Kindler V, Belkouch MC, Dussex G, Tribolet N, et al. B7-homolog 1 expression by human glioma: a new mechanism of immune evasion. Neuroreport. 2005;16(10):1081-5.
21. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005;104(10):2084-91.
22. Schreiner B, Mitsdoerffer M, Kieseier BC, Chen L, Hartung HP, Weller M, et al. Interferon-beta enhances monocyte and dendritic cell expression of B7-H1 (PD-L1), a strong inhibitor of autologous T-cell activation: relevance for the immune modulatory effect in multiple sclerosis. Journal of neuroimmunology. 2004;155(1-2):172-82.
23. Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. Nature medicine. 2007;13(1):84-8.
24. Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2005;11(8):2947-53.
25. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007;13(7):2151-7.
26. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer Immunol Immunother. 2007;56(8):1173-82.
27. Liu J, Hamrouni A, Wolowiec D, Coiteux V, Kuliczkowski K, Hetuin D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood. 2007;110(1):296-304.
28. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annual review of immunology. 2008;26:677-704.
29. Jacobs JF, Idema AJ, Bol KF, Nierkens S, Grauer OM, Wesseling P, et al. Regulatory T cells and the PD-L1/PD-1 pathway mediate immune suppression in malignant human brain tumors. Neuro-oncology. 2009;11(4):394-402.
30. Ishida M, Iwai Y, Tanaka Y, Okazaki T, Freeman GJ, Minato N, et al. Differential expression of PD-L1 and PD-L2, ligands for an inhibitory receptor PD-1, in the cells of lymphohematopoietic tissues. Immunology letters. 2002;84(1):57-62.

31. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. Cancer. 2007;109(8):1499-505.
32. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(9):3360-5.
33. Salih HR, Wintterle S, Krusch M, Kroner A, Huang YH, Chen L, et al. The role of leukemia-derived B7-H1 (PD-L1) in tumor-T-cell interactions in humans. Experimental hematology. 2006;34(7):888-94.
34. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001;2(3):261-8.
35. Tseng SY, Otsuji M, Gorski K, Huang X, Slansky JE, Pai SI, et al. B7-DC, a new dendritic cell molecule with potent costimulatory properties for T cells. The Journal of experimental medicine. 2001;193(7):839-46.
36. Zhong X, Tumang JR, Gao W, Bai C, Rothstein TL. PD-L2 expression extends beyond dendritic cells/macrophages to B1 cells enriched for V(H)11/V(H)12 and phosphatidylcholine binding. European journal of immunology. 2007;37(9):2405-10.
37. Bennett F, Luxenberg D, Ling V, Wang IM, Marquette K, Lowe D, et al. Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses. Journal of immunology. 2003;170(2):711-8.
38. Carter L, Fouser LA, Jussif J, Fitz LJ, Deng B, Wood CR, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. European journal of immunology. 2002;32(3):634-43.
39. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunological reviews. 2008;224:166-82.
40. Nurieva R, Thomas S, Nguyen T, Martin-Orozco N, Wang Y, Kaja MK, et al. T-cell tolerance or function is determined by combinatorial costimulatory signals. EMBO J. 2006;25(11):2623-33.
41. Saunders PA, Hendrycks VR, Lidinsky WA, Woods ML. PD-L2:PD-1 involvement in T cell proliferation, cytokine production, and integrin-mediated adhesion. European journal of immunology. 2005;35(12):3561-9.
42. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. Journal of immunology. 2004;173(2):945-54.
43. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(24):13866-71.
44. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Molecular and cellular biology. 2005;25(21):9543-53.
45. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS letters. 2004;574(1-3):37-41.

46. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity. 1999;11(2):141-51.
47. Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291(5502):319-22.
48. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England journal of medicine. 2012;366(26):2443-54.
49. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. The New England journal of medicine. 2013;369(2):134-44.
50. Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. International journal of radiation oncology, biology, physics. 2013;86(2):343-9.
51. Oganesyan V, Gao C, Shirinian L, Wu H, Dall'Acqua WF. Structural characterization of a human Fc fragment engineered for lack of effector functions. Acta crystallographica Section D, Biological crystallography. 2008;64(Pt 6):700-4.
52. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45(2):228-47.
53. Zhang J, Stevens MF, Bradshaw TD. Temozolomide: mechanisms of action, repair and resistance. Current molecular pharmacology. 2012;5(1):102-14.
54. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. Cancer. 1993;71(8):2585-97.
55. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet. 2002;359(9311):1011-8.
56. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England journal of medicine. 2005;352(10):987-96.
57. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(32):4085-91.
58. Brada M, Hoang-Xuan K, Rampling R, Dietrich PY, Dirix LY, Macdonald D, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol. 2001;12(2):259-66.
59. Brandes AA, Ermani M, Basso U, Amista P, Berti F, Scienza R, et al. Temozolomide as a second-line systemic regimen in recurrent high-grade glioma: a phase II study. Ann Oncol. 2001;12(2):255-7.
60. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer. 2000;83(5):588-93.
61. Perry JR, Belanger K, Mason WP, Fulton D, Kavan P, Easaw J, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(12):2051-7.

62. Walbert T, Mikkelsen T. Recurrent high-grade glioma: a diagnostic and therapeutic challenge. Expert review of neurotherapeutics. 2011;11(4):509-18.
63. Bredel M, Scholtens DM, Harsh GR, Bredel C, Chandler JP, Renfrow JJ, et al. A network model of a cooperative genetic landscape in brain tumors. Jama. 2009;302(3):261-75.
64. Carro MS, Lim WK, Alvarez MJ, Bollo RJ, Zhao X, Snyder EY, et al. The transcriptional network for mesenchymal transformation of brain tumours. Nature. 2010;463(7279):318-25.
65. Network TC. Corrigendum: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2013;494(7438):506.
66. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807-12.
67. Singh D, Chan JM, Zoppoli P, Niola F, Sullivan R, Castano A, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. Science. 2012;337(6099):1231-5.
68. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer cell. 2010;17(1):98-110.
69. Huse JT, Holland EC. Targeting brain cancer: advances in the molecular pathology of malignant glioma and medulloblastoma. Nature reviews Cancer. 2010;10(5):319-31.
70. Wick W, Weller M, Weiler M, Batchelor T, Yung AW, Platten M. Pathway inhibition: emerging molecular targets for treating glioblastoma. Neuro-oncology. 2011;13(6):566-79.
71. De Witt Hamer PC. Small molecule kinase inhibitors in glioblastoma: a systematic review of clinical studies. Neuro-oncology. 2010;12(3):304-16.
72. Plate KH, Breier G, Weich HA, Risau W. Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. Nature. 1992;359(6398):845-8.
73. Folkman J. Tumor angiogenesis: therapeutic implications. The New England journal of medicine. 1971;285(21):1182-6.
74. Folkman J. Angiogenesis: an organizing principle for drug discovery? Nature reviews Drug discovery. 2007;6(4):273-86.
75. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist. 2009;14(11):1131-8.
76. Wick W, Weller M, van den Bent M, Stupp R. Bevacizumab and recurrent malignant gliomas: a European perspective. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(12):e188-9; author reply e90-2.
77. Rinne ML, Lee EQ, Nayak L, Norden AD, Beroukhim R, Wen PY, et al. Update on bevacizumab and other angiogenesis inhibitors for brain cancer. Expert opinion on emerging drugs. 2013;18(2):137-53.
78. Reardon DA, Herndon JE, 2nd, Peters KB, Desjardins A, Coan A, Lou E, et al. Bevacizumab continuation beyond initial bevacizumab progression among recurrent glioblastoma patients. Br J Cancer. 2012;107(9):1481-7.
79. Zuniga RM, Torcuator R, Jain R, Anderson J, Doyle T, Schultz L, et al. Rebound tumour progression after the cessation of bevacizumab therapy in patients with recurrent high-grade glioma. Journal of neuro-oncology. 2010;99(2):237-42.
80. Hodi FS, Lawrence D, Lezcano C, Wu X, Zhou J, Sasada T, et al. Bevacizumab plus ipilimumab in patients with metastatic melanoma. Cancer immunology research. 2014;2(7):632-42.
81. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Current opinion in immunology. 2012;24(2):207-12.

82. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. The New England journal of medicine. 2012;366(10):925-31.
83. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. The New England journal of medicine. 2014;370(8):709-22.
84. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. The New England journal of medicine. 2014;370(8):699-708.
85. Reardon DA, Herndon JE, 2nd, Peters K, Desjardins A, Coan A, Lou E, et al. Outcome after bevacizumab clinical trial therapy among recurrent grade III malignant glioma patients. Journal of neuro-oncology. 2012;107(1):213-21.
86. Kreisl T, Kim L, Moore K, Duic P, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(5):740-45.
87. Griffioen AW. Anti-angiogenesis: making the tumor vulnerable to the immune system. Cancer Immunol Immunother. 2008;57(10):1553-8.
88. Johnson BF, Clay TM, Hobeika AC, Lyerly HK, Morse MA. Vascular endothelial growth factor and immunosuppression in cancer: current knowledge and potential for new therapy. Expert Opin Biol Ther. 2007;7(4):449-60.
89. Ohm J, Carbone D. VEGF as a mediator of tumor-associated immunodeficiency. Immunol Res 2001;23(2-3):263-72.
90. Gabrilovich D, Ishida T, Oyama T, Ran S, Kravtsov V, Nadaf S, et al. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages in vivo. Blood. 1998;92(11):4150-66.
91. Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nature medicine. 1996;2(10):1096-103.
92. Mulligan JK, Day TA, Gillespie MB, Rosenzweig SA, Young MR. Secretion of vascular endothelial growth factor by oral squamous cell carcinoma cells skews endothelial cells to suppress T-cell functions. Hum Immunol. 2009;70(6):375-82.
93. Ohm J, Gabrilovich D, Sempowski G, Kisseleva E, et al. VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression Blood. 2003;101(12):4878-86.
94. Huang X, Raskovalova T, Lokshin A, Krasinskas A, Devlin J, Watkins S, et al. Combined antiangiogenic and immune therapy of prostate cancer. Angiogenesis. 2005;8(1):13-23.
95. Huang Y, Yuan J, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(43):17561-6.
96. Miyazaki J, Tsuzuki Y, Matsuzaki K, Hokari R, Okada Y, Kawaguchi A, et al. Combination therapy with tumor-lysate pulsed dendritic cells and antiangiogenic drug TNP-470 for mouse pancreatic cancer. Int J Cancer. 2005;117(3):499-505.
97. Shrimali R, Yu Z, Theoret M, Chinnasamy D, Restifo N, Rosenberg S. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer research. 2010;70(15): 6171-80.

98. Li B, Lalani AS, Harding TC, Luan B, Koprivnikar K, Huan Tu G, et al. Vascular endothelial growth factor blockade reduces intratumoral regulatory T cells and enhances the efficacy of a GM-CSF-secreting cancer immunotherapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2006;12(22):6808-16.
99. Manning E, Ullman J, Leatherman J, Asquith J, Hansen T, et al. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism Clini Cancer Res 2007;13(13):3951-9.
100. Motz GT, Santoro SP, Wang LP, Garrabrant T, Lastra RR, Hagemann IS, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. Nature medicine. 2014;20(6):607-15.
101. Vredenburgh J, Cloughesy T, Samant M, Prados M, Wen P, Mikkelsen T, et al. Corticosteroid use in patients with glioblastoma at first or second relapse treated with bevacizumab in the BRAIN study. Oncologist 2010;15(12):1329-34.
102. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012;13(5):459-65.
103. de Groot JF, Fuller G, Kumar AJ, Piao Y, Eterovic K, Ji Y, et al. Tumor invasion after treatment of glioblastoma with bevacizumab: radiographic and pathologic correlation in humans and mice. Neuro-oncology. 2010;12(3):233-42.
104. Keunen O, Johansson M, Oudin A, Sanzey M, Rahim SA, Fack F, et al. Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(9):3749-54.
105. Piao Y, Liang J, Holmes L, Zurita A, et al. Glioblastoma resistance to anti-VEGF therapy is associated with myeloid cell infiltration, stem cell accumulation, and a mesenchymal phenotype. Neuro-oncology. 2012;14(11):1379-92.
106. Lu K, Chang J, Parachoniak C, Pandika M, Aghi M, et al. VEGF inhibits tumor cell invasion and mesenchymal transition through a MET/VEGFR2 complex. Cancer cell. 2012;22(1):21-35.
107. DeLay M, Jahangiri A, Carbonell WS, Hu YL, Tsao S, Tom MW, et al. Microarray analysis verifies two distinct phenotypes of glioblastomas resistant to antiangiogenic therapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18(10):2930-42.
108. Jain RK, Tong RT, Munn LL. Effect of vascular normalization by antiangiogenic therapy on interstitial hypertension, peritumor edema, and lymphatic metastasis: insights from a mathematical model. Cancer research. 2007;67(6):2729-35.
109. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005;307(5706):58-62.
110. Sorensen AG, Emblem KE, Polaskova P, Jennings D, Kim H, Ancukiewicz M, et al. Increased survival of glioblastoma patients who respond to antiangiogenic therapy with elevated blood perfusion. Cancer research. 2012;72(2):402-7.
111. Emblem KE, Mouridsen K, Bjornerud A, Farrar CT, Jennings D, Borra RJ, et al. Vessel architectural imaging identifies cancer patient responders to anti-angiogenic therapy. Nature medicine. 2013;19(9):1178-83.
112. Huang Y, Goel S, Duda D, Fukumura D, Jain R. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. Cancer research. 2013;73(10):2943-8.
113. Lorgis V, Maura G, Coppa G, Hassani K, et al. Relation between bevacizumab dose intensity and high-grade glioma survival: a retrospective study in two large cohorts. Journal of neuro-oncology. 2012;107(2):351-8.

114. Ballman KV, Buckner JC, Brown PD, Giannini C, Flynn PJ, LaPlant BR, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro-oncology. 2007;9(1):29-38.
115. Lamborn KR, Yung WK, Chang SM, Wen PY, Cloughesy TF, DeAngelis LM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro-oncology. 2008;10(2):162-70.
116. Wu W, Lamborn KR, Buckner JC, Novotny PJ, Chang SM, O'Fallon JR, et al. Joint NCCTG and NABTC prognostic factors analysis for high-grade recurrent glioma. Neuro-oncology. 2010;12(2):164-72.
117. Taal W, Oosterkamp HM, Walenkamp AM, Dubbink HJ, Beerepoot LV, Hanse MC, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol. 2014;15(9):943-53.
118. Quant E, Norden AD, Drappatz J, Ciampa A, Doherty L, Lafrankie D, et al. Role of a second chemotherapy in recurrent malignant glioma patients who progress on a bevacizumab-containing regimen. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(15S):Abstract at ASCO Annual Mtg.
119. Torcuator RG, Thind R, Patel M, Mohan YS, Anderson J, Doyle T, et al. The role of salvage reirradiation for malignant gliomas that progress on bevacizumab. Journal of neuro-oncology. 2010;97(3):401-7.
120. Reardon D, Desjardins A, Peters K, Gururangan S, Sampson J, Rich JN, et al. Phase II study of metronomic chemotherapy with bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy. Journal of neuro-oncology. 2011;103(2):371-9.
121. Lu-Emerson C, Norden AD, Drappatz J, Quant EC, Beroukhim R, Ciampa AS, et al. Retrospective study of dasatinib for recurrent glioblastoma after bevacizumab failure. Journal of neuro-oncology. 2011;104(1):287-91.
122. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(11):1963-72.
123. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
124. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu M-A, Yung WKA, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. Qual Life Res. 1996;5(1):139-50.
125. Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. European journal of cancer. 2010;46(6):1033-40.
126. Nayak L, DeAngelis LM, Wen PY, Brandes AA, Soffietti R, Peereboom DM, et al. The Neurologic Assessment in Neuro-Oncology (NANO) Scale: A Tool To Assess Neurologic Function for Integration in the Radiologic Assessment in Neuro-Oncology (RANO) Criteria Neuro-oncology. 2013;15(Suppl 3):iii123.
127. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical

cancer research : an official journal of the American Association for Cancer Research. 2009;15(23):7412-20.
128. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. The New England journal of medicine. 2010;363(8):711-23.