Protocol Title:
A phase I/II trial of combination Tumor Treating Fields, Nivolumab plus/minus Ipilimumab for recurrent glioblastoma

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Agent(s):
Tumor Treating Fields (TTFields) via NovoTTF200A (Optune™) Device
Nivolumab (Opdivo™)
Ipilimumab (Yervoy™)

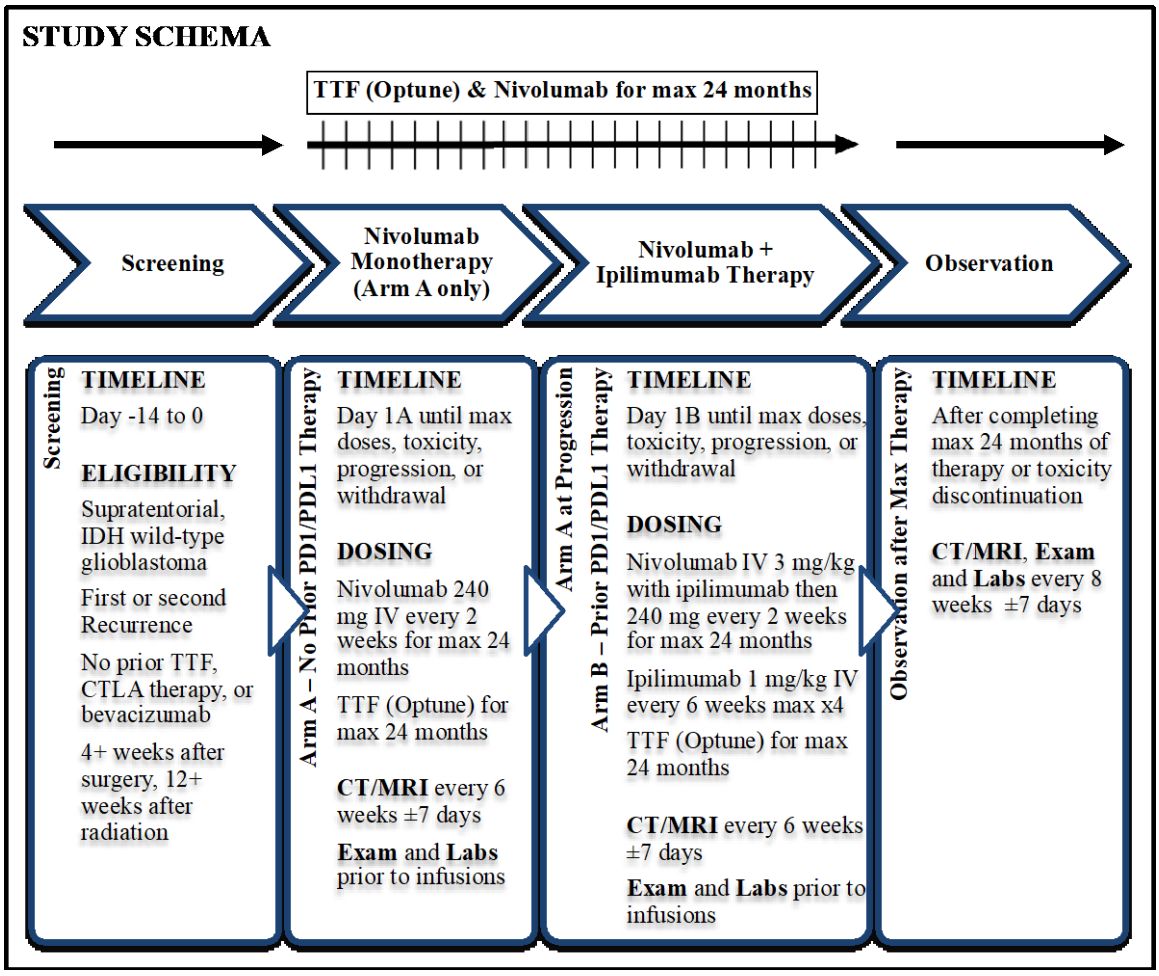
FDA IND Number: 138164

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is an open-label, phase II trial with two parallel arms, two-stage design and appropriate stopping rules for poor efficacy. Arm A will enroll patients without prior PD1/PDL1 checkpoint inhibitor, while Arm B will enroll patients with prior PD1/PDL1 checkpoint inhibitor. We expect to enroll at least 30 (15 in each Arm) and a maximum of 60 (30 in each Arm) evaluable subjects. All subjects will receive TTFields therapy plus nivolumab infusions for a maximum of 24 months, plus/minus concurrent ipilimumab for a maximum of 4 doses (see study schema below).



The NovoTTF200A (Optune™) device is worn continuously for ≥75% of the time, ranging 18 hours/day uninterrupted to 22 hours/day with 2-3 days off monthly. TTFields therapy begins once approved by insurance and an in-home initiation arranged. The goal is to start within 1 month of trial enrollment. Treatment is planned for ~24 months.

Infusions will start within 1 week of study enrollment. Nivolumab will be dosed every 2 weeks IV 240 mg as monotherapy and 3 mg/kg with ipilimumab. Nivolumab therapy will not exceed 24 months. Ipilimumab starts with the second infusion of nivolumab for Arm B (prior PD1/PDL1 checkpoint inhibitor) or after progression on nivolumab monotherapy for Arm A (no prior PD1/PDL1 checkpoint inhibitor). Ipilimumab infusions will be dosed as 1 mg/kg once every 6 weeks for a maximum of 4 doses (24 weeks). Infusions will continue until a maximum of 24 months or when there is confirmed tumor progression, intolerable adverse effects or withdrawal of consent.

All patients will undergo clinical evaluation prior to each infusion every 2 weeks until the maximum 24 months of therapy, thereafter every 8 weeks during the maintenance phase. Neuroimaging studies (contrast-enhanced brain MRI or CT for patients unable to undergo MRI) and quality of life FACT-BR questionnaires will be administered at baseline then every 6 weeks during the treatment phase or every 8 weeks during the maintenance phase until off study.

All subjects will remain on study until death, progressive disease, unacceptable toxicity or withdrawal of consent. If the participant undergoes another surgery for presumed tumor progression but pathological findings are consistent with pseudoprogression (inflammation and necrosis rather than active tumor), the participant will deemed to not have had tumor progression and may continue treatment with nivolumab after review with the principal investigator.

1.2 Primary Objectives

To evaluate the anti-tumor activity of combining TTFields therapy via the NovoTTF200A (Optune™) device, nivolumab, plus/minus ipilimumab therapy as assessed by objective response rate (ORR) by modified immunotherapy iRANO criteria from study enrollment among patients with bevacizumab-naïve, recurrent glioblastoma.

1.3 Secondary Objectives

- Estimate objective response rate (ORR) by standard RANO criteria
- Estimate progression free survival (PFS)
- Estimate overall survival (OS)
- Assess safety
- Assess rates of compliance above the 75% goal for TTFields therapy via the NovoTTF200A (Optune™)
- Assess rates and reasons of discontinuation of any component of therapy
- Exploratory analysis of tumor and serum biomarkers in relation to clinical outcome (ORR, PFS and OS)
- Quality of life assessment based on the Functional Assessment of Cancer Therapy-Brain (FACT-Br)
- Multivariable analyses of prognostic factors, including age, functional status, MGMT hypermethylation status

2. BACKGROUND

2.1 Glioblastoma Overview

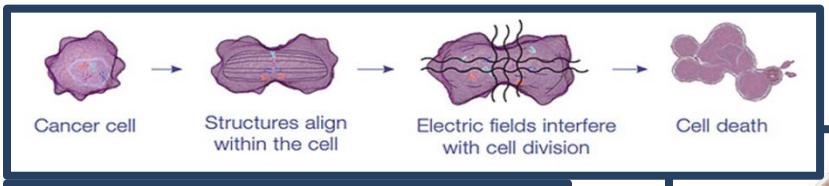
In 2014, 23,300 patients were newly diagnosed with a central nervous system (CNS) cancer, while 14,000 deaths were attributed to CNS malignancy (Siegel et al., 2014). Glioblastoma is the most common and lethal primary CNS malignancy and comprises 15% of all brain cancers (Patel et al., 2014). The 3- and 5-year survival rate for glioblastoma remain at ~10-15% and ~1-5%, respectively (Stupp et al., 2009). Glioblastoma remains a significant unmet clinical need with dismal survival and limited effective treatment options. There is an urgent and unmet need for innovative, safe, and effective therapy combinations for glioblastoma.

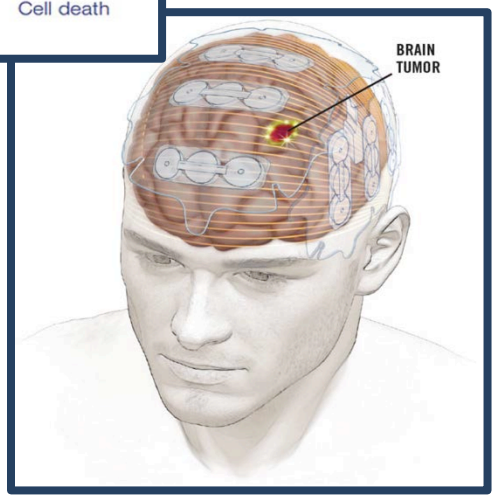
2.2 Tumor Treating Fields (TTFields) Therapy using NovoTTF-200A (Optune™) Device

Refer to the Investigator's Brochure (IB) for detailed preclinical and clinical data.

2.2.1 Background

NovoTTF-200A (Optune™) is a portable battery operated device that produces TTFields within the human body by means of surface electrodes. The TTFields are applied to the patient by means of surface electrodes that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient.





The electrodes are placed on the patient's shaved head over a layer of adhesive hydrogel and held in place with hypoallergenic medical tape. The electrodes must be replaced every 3-4 days and the scalp re-shaved in order to maintain optimal capacitative coupling between the electrodes and the patient head. All the treatment parameters are pre-set by Novocure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external plug in power supply.

These alternating electrical fields physically interfere with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase. This causes failure of cytokinetic furrow formation and resultant mitotic blebbing, leading to the disruption of chromosome segregation and eventual cell death (Kirson et al., 2007; Kirson et al., 2004). The exact pathways by which spindle disruption and physical aggregation of macromolecules lead to cell death are unknown. TTFields therapy has been tested in several pilot clinical studies including small single arms study as monotherapy for recurrent glioblastoma and for newly diagnosed glioblastoma. More recently, 2 large phase III trials have been completed. TTFields therapy has been approved for recurrent glioblastoma since 2011.

2.2.2 Clinical Data

- **EF-11 Phase III trial comparing NovoTTF-100A monotherapy to physician's choice chemotherapy in recurrent glioblastoma**

  This randomized trial compared standard chemotherapy per local practice (active

treatment control group) with NovoTTF-200A in a prospective, multicenter phase III trial. This international clinical study enrolled 237 patients with recurrent glioblastoma or with glioblastoma that hadn't responded to traditional therapy. Patients in the study were randomly assigned to receive either the NovoTTF-200A System or chemotherapy treatment. The study showed comparable overall survival rates between patients treated with the NovoTTF-200A System and those who underwent chemotherapy (Stupp et al., 2012).

This new minimally invasive and chemotherapy-free local treatment modality demonstrated a statistically non-significant increased response rate (14 versus 9.6%, $p = 0.19$), an improved PFS6 rate (21% versus 15%, $p = 0.13$), and a trend towards reduction of the risk of death (hazard ratio 0.86, 95% CI 0.66–1.12, $p = 0.27$), as well as sustained improvement in quality of life. In addition, there was improvement in the cognitive and emotional functions in the NovoTTF-200A arm compared to chemotherapy. Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of NovoTTF-100 patients. This condition was easily treated with topical corticosteroids, resolved completely after treatment and did not require substantial treatment breaks. However, they did not experience the significant side effects associated with chemotherapy, including nausea, anemia, fatigue and serious infections. In 2011, the FDA based its approval of the NovoTTF-200A System for recurrent glioblastoma on results from this study.

- **EF-14 Phase III prospective multicenter trial of NovoTTF-200A with temozolomide compared to temozolomide alone in patients with newly diagnosed glioblastoma**

  This is a prospective randomized open-label phase III study of NovoTTF-200A concomitant with temozolomide versus temozolomide alone after standard radiation and temozolomide for newly diagnosed glioblastoma. The trial was designed to randomize 700 patients in a 2:1 ratio and the primary endpoint was progression-free survival but study was also powered for overall survival.

  A pre-specified interim analysis was performed on the first 315 patients randomized (210 on the temozolomide and NovoTTF-200A, 105 on temozolomide only). The median PFS was 3.9 months in the temozolomide group and 7.1 months in the NovoTTF-200A concomitant with temozolomide (p=0.0013). The 1-year survival was 68.3% in the temozolomide alone arm and 74.5% in the NovoTTF-200A concomitant with temozolomide arm. The median survival times were 15.6 months and 20.5 months (p=0.0042), respectively. In addition, there was no concern raised by the review of the safety data on these patients and no new significant toxicity was described in the NovoTT-200A group. These interim analyses led the independent DSMC to suspend enrollment in the trial and permit patients randomized to temozolomide alone to receive NovoTTF-200A.(Stupp et al., 2015) The results of this trial led to FDA approval of NovoTTF-200A for newly diagnosed glioblastoma patients.

2.2.3 Safety Profile

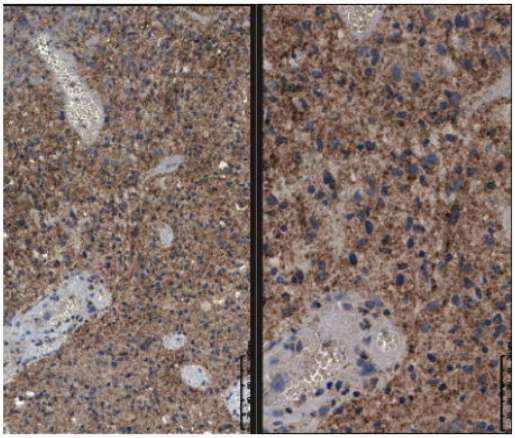
Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of NovoTTF-100 patients in the EF-11 trial, and 44% of patients in the EF-14 trial. This condition was easily treated with topical corticosteroids, resolved completely after treatment, was stopped and did not require substantial treatment breaks. The risk of headaches, seizures or cerebral edema does not seem to be increased in patients on NovoTTF-200A.

2.3 Rationale for Immunotherapy in Glioblastoma

Modified from Sampson J, et al. ASCO 2015: Preliminary Safety and Activity of Nivolumab and its Combination with Ipilimumab in Recurrent Glioblastoma: CHECKMATE-143 (NCT02017717)

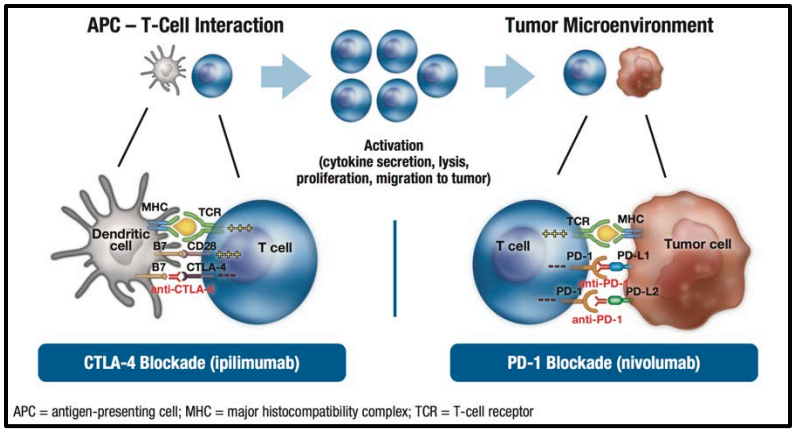
Immunologic factors have been clinically associated with gliomas. A reduced risk of gliomas and longer survival is associated with elevated immunoglobulin (Ig) E levels compared to normal (Schwartzbaum J, et al. J NCI 2012; Turner MC. Cancer Immunol Immunother 2012; Lin Y, et al. Chin Med J (Engl) 2011; Schlehofer B, et al. Allergy 2011). Programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are immune checkpoint receptors that regulate immunity. Binding of PD-1 with its ligands, PD-L1 and PD-L2, downregulates the T cell immune function (Yao Y, et al. Neuro Oncol 2009). PD-1 is expressed on tumor-infiltrating lymphocytes whereas PD-L1 is expressed on tumor cells and microglia in most glioblastomas (Yao Y, et al. Neuro Oncol 2009). Diffuse fibrillary expression of PD-L1 is evident in both newly diagnosed and recurrent glioblastoma (Figure A; Berghoff AS, et al. J Clin Oncol 2014; Berghoff AS, et al. Neuro Oncol 2015). PD-L1 expression correlates with malignancy grade of gliomas (Yao Y, et al. Neuro Oncol 2009). CTLA-4 signaling attenuates the immune response by increasing the T-cell activation threshold and potentially increasing activity of suppressor T cells (Riley JL, June CH. Blood 2005).

A. Diffuse Fibrillary Expression of PD-L1



Newly diagnosed GBM	>25% of tissue	103/117 (88%)
Recurrent GBM	>25% of tissue	13/18 (72%)

In a murine model of glioblastoma, antibodies that inhibit PD-1 can prolong survival. Preclinical studies in mice showed that combined PD-1/CTLA-4 blockade was more effective than either agent alone at increasing tumor infiltration of T-effector cells and decreasing T-regulatory cell numbers (Curran MA, et al. Proc Natl Acad Sci USA 2010). Nivolumab is a fully human, IgG4 monoclonal antibody that targets the PD-1 immune checkpoint pathway and prevents binding of PD-1 with PD-L1 and PD-L2. Ipilimumab is a fully humanized IgG1 monoclonal antibody that binds to CTLA-4. Figure depicts the mechanisms of action (modified from Pillai RN, et al. AACR 2017: CHECKMATE-817 (NCT02869789)). Patients with melanoma brain metastases had objective responses to ipilimumab, suggesting efficacy in the central nervous system (Margolin K, et al. Lancet Oncol. 2012). Combination immunotherapy with nivolumab and ipilimumab may improve outcomes for patients with recurrent glioblastoma, while early phase studies reveal tolerable toxicity profile comparable to other tumor types.



APC = antigen-presenting cell; MHC = major histocompatibility complex; TCR = T-cell receptor

2.4 Nivolumab

Refer to the Investigator's Brochure (IB) for detailed background information.

2.4.1 Background

An intact immune surveillance is important in controlling outgrowth of neoplastic transformation. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member that is related to CD28 and CTLA-4 and that negatively regulates antigen receptor signaling upon binding to its ligands (PD-L1 and/or PD-L2). The murine PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regulatory and Natural Killer cells. PD-1 is also expressed during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or induced in a variety of cell types, including non-hematopoietic tissues and various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and containing short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, particularly vascular endothelium. PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers express abundant levels of this T-cell inhibitor. PD-1 may also regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway is critical tumor immune evasion and, thus, an attractive therapeutic target.

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Opdivo™ (nivolumab) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Nivolumab has been approved as monotherapy for:

- Metastatic melanoma
- Metastatic non-small cell lung cancer (NSCLC) progressing on or after platinum-based chemotherapy
- Advanced renal cell carcinoma after anti-angiogenic therapy
- Classical Hodgkin lymphoma relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT,
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing on or after a platinum-based therapy
- Locally advanced or metastatic urothelial carcinoma progressing on or within 12 months of platinum-based chemotherapy

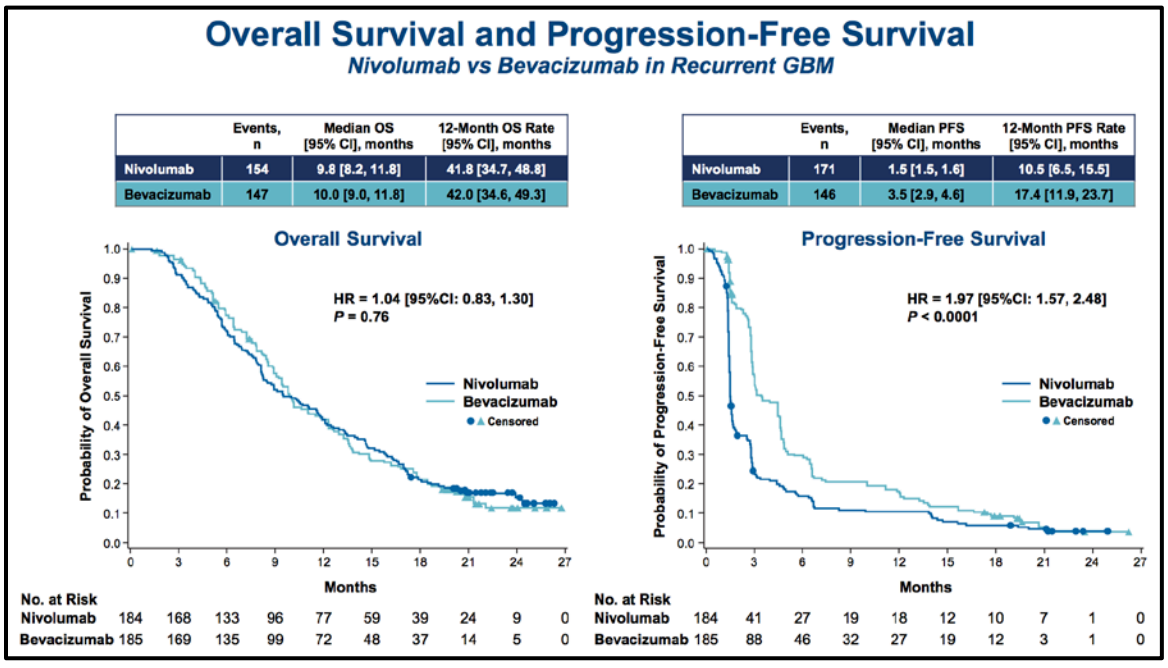
Opdivo™ (nivolumab) has also been approved as in combination with ipilimumab for metastatic melanoma. Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies, and as single-dose monotherapy for the treatment of sepsis.

2.4.2 Preclinical and Clinical Data

Refer to the Investigator's Brochure (IB) for Preclinical and Clinical details.

2.4.3 Clinical Activity in Subjects with Glioblastoma

Cohort 2 of CheckMate 143 (CA209143) was a randomized phase 3, open-label study comparing nivolumab monotherapy with bevacizumab for recurrent glioblastoma. Toxicity profile was comparable to other cancers. Nivolumab did not meet the primary endpoint of superior OS when compared with bevacizumab (HR = 1.04; P = 0.76, see Figure below).



Objective response rate (ORR) with nivolumab was lower than bevacizumab (7.8% vs. 23.1%), while stable disease was noted in 21.6% and 46.8%, respectively. There was a longer time to best response (3.0 vs. 1.5 months) as well as prolonged response duration (11.1 vs. 5.3 months) with nivolumab compared to bevacizumab. As a single agent, nivolumab revealed minimal and delayed but durable response in recurrent glioblastoma

2.4.4 Pharmacokinetic Studies
Refer to the Investigator's Brochure (IB) for Pharmacokinetic data.

2.4.5 Safety Profile
Refer to the Investigator's Brochure (IB) for Pharmacokinetic data.

Most common adverse reactions (≥20%) in patients treated with nivolumab as monotherapy, included fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia. In combination with ipilimumab, the most common reactions were fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea.

Nivolumab should be withheld for moderate and permanently discontinued for any of the following serious or life-threatening adverse reactions: pneumonitis, colitis, hepatitis (transaminase or total bilirubin elevation), nephritis and renal dysfunction, hypophysitis, adrenal insufficiency, encephalitis, or infusion reactions.

Patients with prior allogeneic HSCT should be monitored for signs of hyperacute, grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. Nivolumab can cause fetal harm.

2.5 Ipilimumab

Refer to the Investigator's Brochure (IB) for detailed background information.

2.5.1 Background
Ipilimumab (also known as BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4, cluster of differentiation [CD] 152) expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity.
Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 augments T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which contribute to an increase in T-cell responsiveness, including the anti-tumor response.

Yervoy™ (ipilimumab) 3 mg/kg is approved for use in advanced melanoma in over 47 countries, including the United States (US, 25-Mar-2011), the European Union (EU, 13-Jul-2011), and Australia (Jul-2011). Yervoy™ (ipilimumab) 10 mg/kg is approved as adjuvant treatment of unresectable or metastatic melanoma in the US.

2.5.2 Preclinical and Clinical Data
Refer to the Investigator's Brochure (IB) for Preclinical and Clinical details.

Ipilimumab is being investigated in various non-melanoma cancers as monotherapy or in combination with other therapies, including multiple phase I/II studies in patients with glioblastoma.

2.5.3 Pharmacokinetic Studies

Refer to the Investigator's Brochure (IB) for Pharmacokinetic data.

2.5.4 Safety Profile

Refer to the Investigator's Brochure (IB) for Toxicity data.

Blockade of CTLA-4 by ipilimumab leads to T-cell activation, inflammatory adverse events, primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine glands (e.g., hypophysitis and adrenal or thyroid abnormalities), and other less frequent organs (e.g., uveitis/episcleritis). Most occur from treatment onset, but few occur weeks to months after discontinuation. Most are reversible with dose modifications, interruptions or discontinuation. In rare cases, these inflammatory toxicities prove fatal.

Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy. Comprehensive metabolic panels (including liver function, adrenocorticotropic hormone [ACTH] level, and thyroid function tests) should be evaluated at baseline and before each dose of ipilimumab. It is advised to rule-out alternative etiologies for any suspected inflammatory toxicity. In general, for severe inflammatory or life-threatening adverse effects, ipilimumab should be permanently discontinued and systematic high-dose corticosteroid initiated. For moderate immune-mediated toxicities, ipilimumab should be held or delayed, and moderate-dose corticosteroids considered.

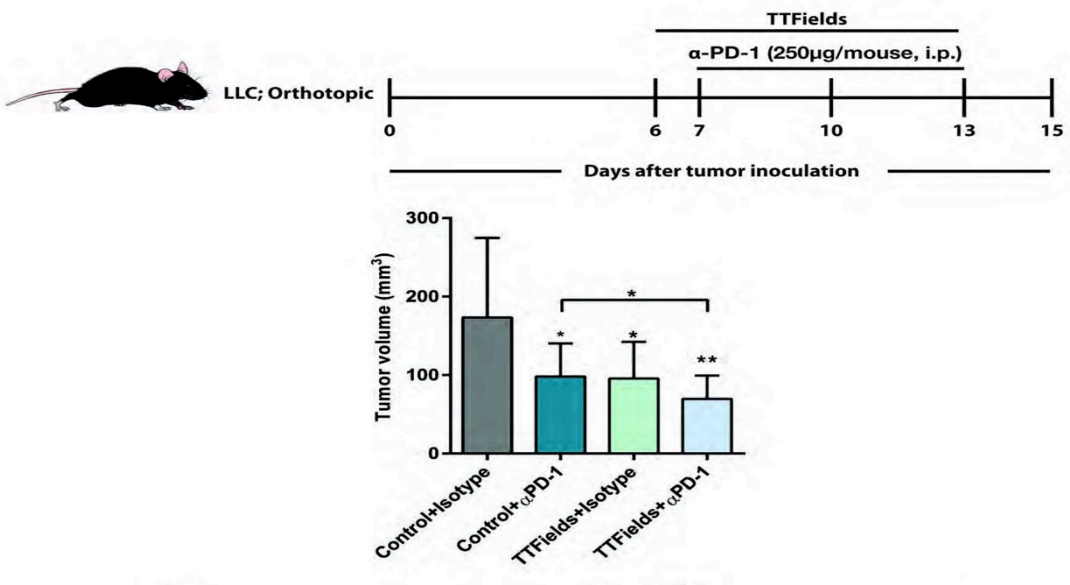
Based on limited clinical experience, corticosteroids do not seem to limit anti-tumor response, e.g. disease control was maintained in subjects with objective responses who received corticosteroid administration for concomitant serious inflammatory AEs.

2.6 Rationale for Combination of TTFields and Immunotherapy

The possible synergism between TTFields and Immunotherapy in preclinical studies and a retrospective glioma cohort warrants study in clinical trials

2.6.1 Preclinical Data

TTFields therapy exhibits treatment duration-dependent intrinsic cytotoxic property toward cancer cells (Stupp et al, Eur J Cancer 2012; Stupp et al, JAMA 2016). The cellular response to TTFields application is characterized by exposure of calreticulin on the cell surface, release of HMGB1, and secretion of ATP—all of which are hallmark features of immunogenic cell death that can potentially generate a systemic anticancer immune response (Gilad et al, Poster: AAI 2016). Immunotherapy shows promise for various tumor histologies in multiple clinical trials. Combining TTFields with anti-PD-1 may achieve tumor control by further enhancing antitumor immunity (Figure 1: Gilad et al, Poster: AAI 2016).



TTFields in Combination With Anti-PD-1 Are Therapeutically Effective in Vivo
For in vivo experiments, 10-12-week-old male C57Bl/6 mice were injected directly into the lungs with Lewis lung carcinoma (LLC-1; 3x103 cells) (Figure 1A). Application of TTFields to the mouse lungs was initiated 6 days afterwards and maintained for 7 days. Mice received an I.P. injection of anti-PD-1 (αPD-1; RMP1-14; 250 μg) or Rat IgG2a (2A3; 250 μg) (Bioxcell), as indicated in the scheme. The combined treatment of TTFields and anti-PD-1 led to a significant decrease in tumor volume as compared to control mice and to mice treated with anti-PD-1 alone (Figure 1B).
Modified from Gilad et al, AAI 2016.

2.6.2 Clinical Data

Tumor-treating fields (TTFields) are approved for use in patients with glioblastomas at recurrence (2011) or adjuvant setting (2016) due to overall survival benefit in various trials. In the EF11 study for recurrent glioblastoma, TTFields monotherapy showed a response rate of 14% compared to <5% response for any salvage therapy as per physician preference, including CCNU, bevacizumab, etc. (Stupp et al, Eur J Cancer 2012). The phase III (EF-14) trial for newly diagnosed glioblastoma also revealed an increase in median survival from 19.8 to 24.5 months for patients treated with adjuvant TTFields and temozolomide versus temozolomide alone.

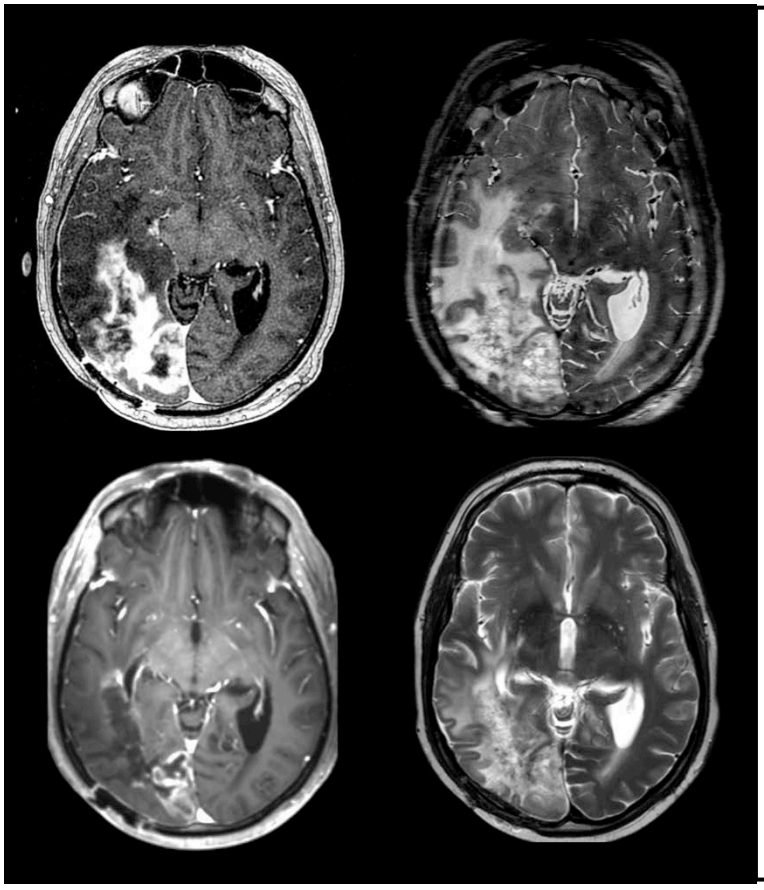
Given preliminary preclinical data demonstrating synergy between TTFields and checkpoint immunotherapy, the rates and outcomes of combination TTFields and immunotherapy were analyzed in a retrospective gliomas cohort (Odia et al, Posters: SNO 2016 and AACR 2017; Schulte et al, SNO 2017).

Since 12/2012, 52 patients with newly diagnosed or recurrent gliomas were treated with TTFields therapy at Columbia University. Of 52 treated patients, 21 (40%) were women and 3 (6%), 5 (10%) and 43 (84%) had WHO grade II, III and IV gliomas, respectively. Median age at diagnosis was 58 (23-84) years. TTFields therapy was used at recurrence in 42 (81%), with a range of 0-4 prior recurrences. Prior therapies included bevacizumab (21, 20%), resection [gross total in 28 (54%)], radiation [mainly 60 Gy in 30 fractions, 44 (85%)] and temozolomide (100%). Median duration of TTFields therapy was 2.4 (0.1-20.3) months. Eleven (21%) patients met the TTFields compliance goal of 75%. Concurrent systemic therapy was used in 40 (77%), including

temozolomide (16, 31%), nitrosourea (4, 8%), bevacizumab (19, 37%), or checkpoint immunotherapy (28, 54%). Nivolumab was the predominant immunotherapy used and dosed 240 mg every 2 weeks. Only 2 (4%) experienced skin toxicity requiring TTFields therapy interruption.

Progression free (PFS) and overall (OS) survival among all patients was 3.6 and 21.5 months, respectively. Median PFS was significantly increased among glioblastoma patients treated with concurrent immunotherapy (4.6 vs. 3.5 months, p=0.04). There was a trend toward increased overall survival after TTFields therapy with addition of immunotherapy (8.3 vs. 6.5 months, p=0.32).

Objective response rate (ORR: defined as complete response, partial response or stable disease for 6 months) based on RANO was increased in patients treated with concurrent immunotherapy versus all other antineoplastic therapy (26% vs. 13%). This is greater than the 14% reported in the phase II EF-11 trial of NovoTTF100A monotherapy (Stupp et al, Eur J Cancer 2012) or the <5-10% objective response seen for early phase trials of checkpoint inhibitor monotherapy, including nivolumab, for recurrent glioblastoma (Preusser et al, Nat Rev Neurol 2015).



Example of Radiographic Response
A patient with recurrent glioblastoma experienced clinical improvement and marked partial response on combination NovoTTF200A (Optune™) and nivolumab. Pre-treatment post-gadolinium T1 (A) and T2 (B) compared to post-treatment post-gadolinium T1 (C) and T2 (D) are shown.

TTFields therapy improves survival for patients with glioblastomas. Immunotherapy also shows promise in various neoplasms. The possible synergism between these modalities in preclinical studies and the retrospective glioma series warrants further study as proposed.

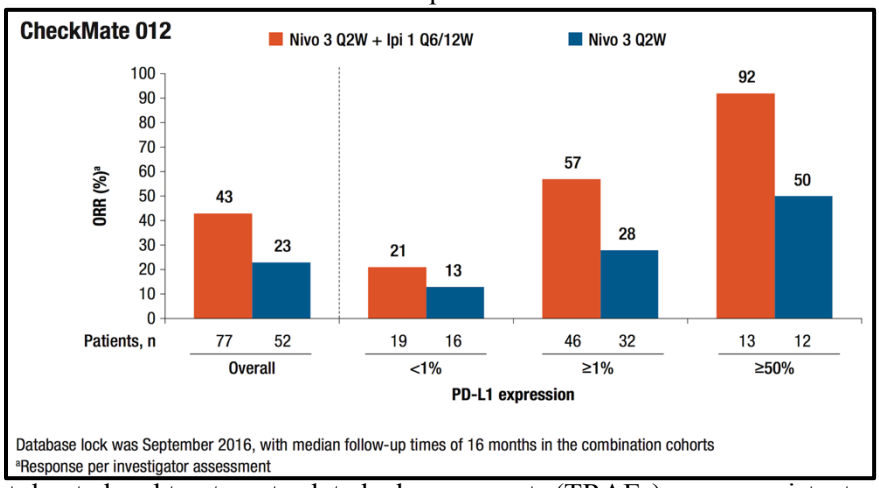
2.6.3 Rationale for dose schedule

A phase I trial of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by maintenance nivolumab 3 mg/kg every 2 weeks revealed tolerable immune-related

toxicity profiles among patients with recurrent glioblastoma and comparable to other tumor types (Sampson J, et al. ASCO 2015: CHECKMATE-143 (NCT02017717) glioblastoma arm). The most common causes of discontinuation were AEs: diarrhea, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, lipase increased, diabetic ketoacidosis, hypocalcemia, hypomagnesemia, hyperthyroidism, cholecystitis, and sepsis.

Another multi-cohort phase 3b/4 trial assessed the efficacy of nivolumab IV 240 mg every 2 weeks plus a maximum of 4 doses of ipilimumab IV 1 mg/kg every 6 weeks followed by maintenance nivolumab for a maximum of 24 months in patients with stage IIIb to IV non-small cell lung cancer (NSCLC), newly diagnosed or recurrent after platinum-based therapy (Pillai RN, et al. AACR 2017: CHECKMATE-817 (NCT02869789)). The study revealed a tolerable toxicity profile comparable to monotherapy profiles, with discontinuation rates of 12% for any grade or grade 3-4 treatment related toxicities. Objective response rates (ORR) were improved for the combination of nivolumab and ipilimumab compared to nivolumab monotherapy. Efficacy measures were comparable to more intense dosing regimens.

CheckMate 012 was a multi-cohort phase 1 trial of nivolumab as monotherapy or in combination with other agents in chemotherapy-naïve patients with NSCLC The combination of nivolumab (3 mg/kg) every 2 weeks (Q2W) plus ipilimumab (1 mg/kg) every 12 or 6 weeks (Q12W or Q6W) showed promising efficacy. Nivolumab in combination with ipilimumab was well tolerated and treatment-related adverse events (TRAEs) were consistent with the known safety profiles of the individual agents. The discontinuation rates attributable to TRAEs in the nivolumab plus ipilimumab cohorts were similar to nivolumab monotherapy (12% for any grade and 12% for grade 3/4). No treatment-related deaths occurred at the time of analysis.



The combination of nivolumab (3 mg/kg) every 2 weeks plus ipilimumab (1 mg/kg) every 6 weeks as the proposed has been well-tolerated, while nivolumab is approved and proven safe as monotherapy when dosed as 240 mg every 2 weeks. Hence, this study utilizes distinct dosing schedules for nivolumab when dosed as monotherapy versus in combination with ipilimumab based on approved and proven safe dosing.

2.7 Correlative Studies Background

Archival tumor tissue will be collected to evaluate molecular predictors of outcome such as MGMT promoter methylation, PDL-1 tumor expression, and tumor mutational load as per available funding.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

1. Male or female patients with age ≥18 years.

2. Histologically confirmed World Health Organization Grade IV glioblastoma with supratentorial distribution.

3. Unequivocal evidence of progressive disease on contrast-enhanced brain CT or MRI as defined by RANO criteria, or documented recurrent glioblastoma on biopsy.

4. Measurable disease based on RANO criteria.

5. Prior therapies including radiation and temozolomide.

6. Any number of recurrences are allowed. Resection of recurrent glioblastoma is not considered a prior treatment.

7. From the projected start of study treatment, the following periods must have elapsed: 4 weeks from any investigational agent, 4 weeks from cytotoxic therapy (except 23 days for temozolomide and 6 weeks from nitrosoureas), or 4 weeks from any other antibodies or any other antineoplastic therapies.

8. Must be at least 12 weeks from radiotherapy or progression outside of the high-dose radiation target volume or unequivocal evidence of progressive tumor on biopsy.

9. All adverse events Grade > 1 related to prior therapies (chemotherapy, radiotherapy, and/or surgery) must be resolved, except for alopecia.

10. Karnofsky Performance Status (KPS) ≥ 60 (see Appendix A).

11. Adequate organ and marrow function as defined below, all screening labs should be performed within 14 days of treatment initiation:
    - absolute neutrophil count ≥ 1,000/mcL
    - platelets ≥ 100,000/mcL
    - hemoglobin > 8.0 mg/dL
    - total bilirubin ≤ 2.0 x upper limit of normal
    - AST (SGOT)/ALT (SGPT) ≤2.5 × upper limit of normal
    - creatinine or creatinine clearance ≥60 mL/min/1.73 m^2 for creatinine >ULN

12. Corticosteroid dose must be stable or decreasing for at least 5 days prior to enrollment.

13. Nivolumab and ipilimumab are potentially teratogenic or abortifacient. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to entry and for the duration of study. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Male subjects should agree to use adequate method of contraception starting with the first dose through 7 months after the last dose of therapy.

14. Brain CT or MRI within 14 days prior to start of study drug.

15. Archival tissue for evaluation of correlative objectives (if available).

16. Ability to understand and the willingness to provide written informed consent.

3.2 Exclusion Criteria

1. Infratentorial disease

2. Bevacizumab within 2 months of enrollment. Prior use of ipilimumab or other CTLA-4 inhibitor or prior TTFields.

3. Tumors with known *IDH1* (isocitrate dehydrogenase 1) or *IDH2* mutations as determined by immunohistochemistry for the *IDH1* R132H variant or by direct sequencing. *IDH1/2*-mutant gliomas have a prolonged overall survival rate compared to *IDH1/2*-wildtype gliomas (Parsons et al., 2008; Yan et al., 2009), indicating distinct natural history.

4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab or ipilimumab or their excipients.

5. Current or planned participation in a study of an investigational agent or using an investigational device.

6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

7. Active or life-threatening infection requiring intravenous or >2 weeks of systemic therapy.

8. Prior stereotactic radiotherapy, convection enhanced delivery (CED) or brachytherapy requires a biopsy to confirm radiographic progression is consistent with progressive tumor and not treatment-related necrosis unless the recurrent lesion is outside of any prior high-dose radiation target volume or distant from the prior CED or brachytherapy site.

9. There is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, so breastfeeding must be discontinued by enrollment on study.

10. Uncontrolled HIV or AIDS is not allowed. Patients with known history of HIV but with undetectable viral load on antiretroviral therapy are allowed.

11. CHF, or MI or hemorrhagic/ischemic stroke in the last 3 months

12. Active illicit drug use or diagnosis of alcoholism

13. Known additional malignancy that is progressing or requires active treatment within 3 years of start of study drug. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, *in situ* cervical cancer or other *in situ* malignancy that has undergone potentially curative therapy and/or with >90% probability of survival beyond 5 years.

14. Any surgery (not including minor diagnostic procedures such as lymph node biopsy) within 2 weeks of start of treatment. Incomplete recovery from any side effects of previous procedures

is also exclusionary.

15. Any significant autoimmune disorders expected to impact multiple or internal organs, excluding mild eczema or autoimmune thyroiditis treated with thyroidectomy and requiring systemic immunosuppressive or immunomodulatory therapy.

16. Any implanted programmable cranial device, including reprogrammable ventriculoperitoneal shunt (VPS) or cochlear implants, that precludes use of TTFields (Optune) therapy.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

Each institution will register eligible participants per local registration procedures. The investigator is responsible for enrolling only those patients who have met all eligibility criteria.

5. TREATMENT PLAN

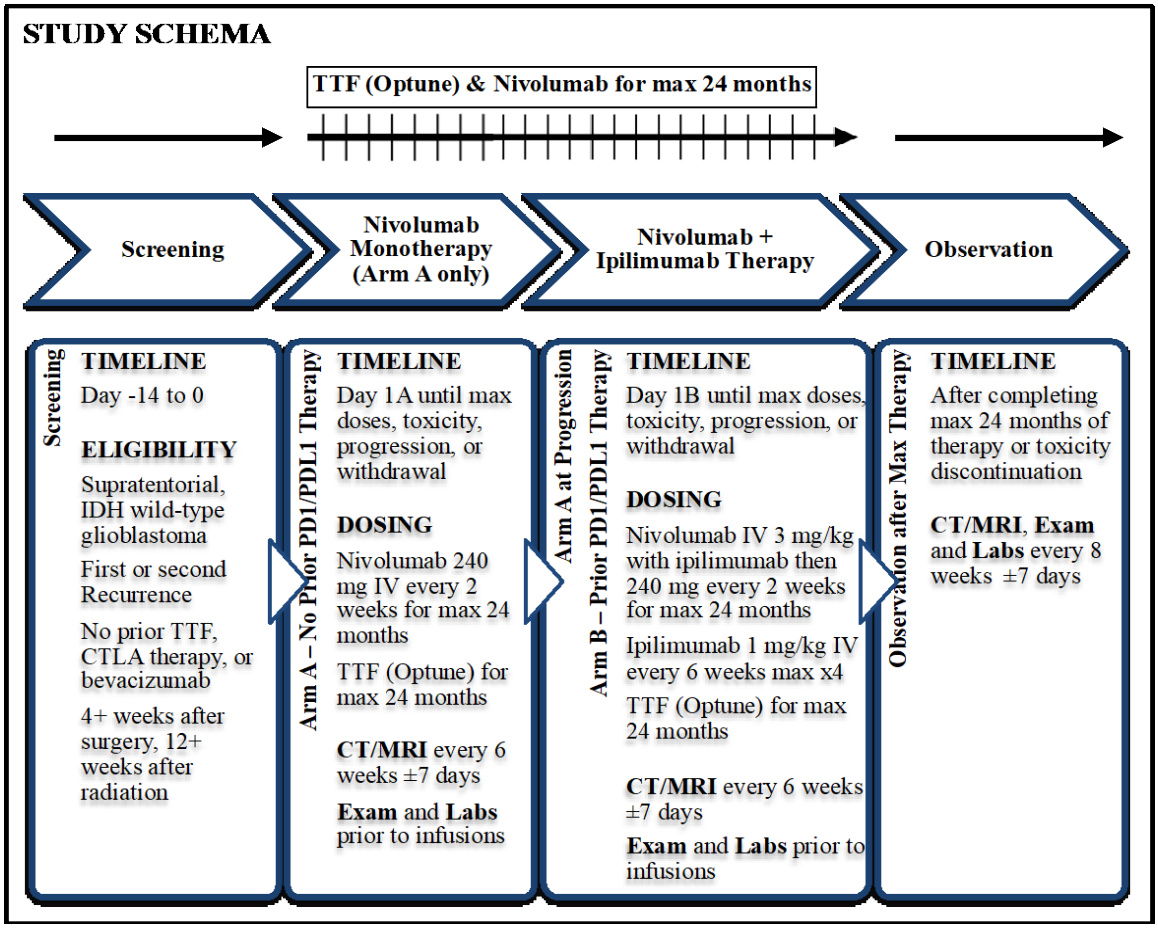
5.1 Study Design

This is an open-label Phase II trial with two parallel arms, two-stage design with appropriate stopping rules for poor efficacy. Arm A will enroll patients without prior history of any PD1/PDL1 checkpoint inhibitor, while Arm B will enroll patients with prior PD1/PDL1 checkpoint inhibitor. We expect to enroll at least 30 (15 in each Arm) and a maximum of 60 (30 in each Arm) evaluable subjects on this study. The study schema is depicted below.

NovoTTF200A (Optune) is a device to be worn continuously for a goal of ≥75% of the time, ranging from 18 hours daily nonstop or 22 hours daily with 2-3 days off monthly. Patients will be encouraged to meet compliance goals via timely feedback and troubleshooting concerns. TTFields therapy begins once approved by insurance and an in-home initiation visit scheduled. The goal is to start within 1 month of starting immunotherapy infusions. Treatment is planned for ~24 months.

Infusions will start within 14 days of sreening/baseline visits. Nivolumab will be dosed every 2 weeks IV 240 mg as monotherapy and 3 mg/kg with ipilimumab. Nivolumab will not exceed 48 doses (24 months). Ipilimumab starts with the second infusion of nivolumab for Arm B (prior immunotherapy) or after progression on single agent nivolumab for Arm A (no prior immunotherapy). Ipilimumab infusions will be dosed as 1 mg/kg once every 6 weeks for a maximum of 4 doses (24 weeks).

Infusions will continue until maximum duration of ipilimumab and nivolumab therapy or when there is confirmed tumor progression, death, intolerable adverse effects or withdrawal. After the maximum of 24 months of therapy, clinical, radiographic and quality of life assessments are performed every 8 weeks until or when there is confirmed tumor progression, death, or withdrawal. One treatment cycle is defined as 6 weeks for the initial 24 months, thereafter every 8 weeks will define observation cycles.



Reported adverse events and potential risks are described in Section 7. Dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-Treatment Criteria

All patients must sign an informed consent prior to any study-specific procedure.
For screening, patients will have the following tests done at the treating institution or in a local lab within 14 days of treatment initiation:

Hematology Panel	**Blood Chemistry Panel**	**Others**
ANC	AST (SGOT)	Pregnancy test (blood)
Platelet count	ALT (SGPT)	Urine analysis
Hematocrit	Creatinine and BUN	PT, PTT, INR
Hemoglobin	Total/direct bilirubin	TSH and free T4
RBC	Alkaline phosphatase	LDH
WBC with differential	Calcium	ACTH
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Random glucose	
	Total protein and Albumin	

Hematologic lab values should be re-evaluated on cycle 1 day 1 and need to meet eligibility parameters to start treatment.

Patients will undergo complete history, including concomitant medications, physical examination, measurement of vital signs (pulse, sitting or supine blood pressure, respiratory rate, temperature) and weight, and clinical assessment of Karnofsky performance status (KPS).
Patients must have had a contrast-enhanced brain MRI or CT scan within 14 days of starting study drug. Measurable disease is required for enrollment.

5.3 Treatment and Evaluation/ Observation Cycles

Blood draws are also performed within 2 days of each infusion. Screening/ Baseline lab results may be used for C1D1 if performed within 14 days of initial treatment. Hematology and blood chemistry panel results must be reviewed by an investigator prior to each infusion. After the maximum of 24 months of therapy, blood draws will only be performed with every clinical and radiographic assessment every 8 weeks.

Prior to each infusion every 2-3 weeks and beyond the initial 24 months every 8 weeks, patients will undergo physical examination, neurological exam, and KPS assessment. Response assessment by MRI or CT and FACT-BR quality of life questionnaires will be performed every 6 weeks for the initial 24 months of therapy and thereafter every 8 weeks. Targeted questioning will collect adverse events and concomitant medications.

To confirm objective response (OR), partial or complete response (see section 11.1 for definitions) by tumor measurements must be confirmed by repeat assessments performed ≥4 weeks after the criteria for response are first met. Progression should also be confirmed by repeat scans ≥4 weeks after progression first suspected on MRI or CT.

If the participant undergoes another surgery for presumed tumor progression, but pathological findings are consistent with pseudoprogression, the participant will be deemed to not have had tumor progression and may continue treatment with nivolumab after principal investigator review.

5.4 End of Treatment Visit

For patients who come off study for toxicity or withdrawal of consent, tumor imaging is at the judgment of the investigator, suggested every 8-12 weeks in the appropriate setting after termination of the study therapy.

If patients come off treatment for progression of disease (Arm B only), intolerance, or withdrawal, they will be seen for assessments of efficacy and safety.

Patients will have repeat safety labs, a clinical examination, weight and KPS assessments, and concurrent medications within 30 days of the last infusion.

If tumor assessments are not done within 4 weeks, these will be obtained within the next 2 weeks after the End of Treatment Visit. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring and 100 days for serious adverse event reporting. Participants removed from protocol therapy for unacceptable adverse events (Section 7) will be followed until resolution or stabilization of the adverse event.
Subjects who discontinue for reasons other than progressive disease will have post-treatment

follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. Subjects will be followed for survival every 2-3 months for a minimum of 1 year, or indefinitely until death or loss to follow-up.

5.5 General Concomitant Medication and Supportive Care Guidelines

Any medication taken by a subject during the course of the study and the reason for its use will be documented in the clinical source documentation.

5.5.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended if the events are suspected as related to nivolumab or ipilimumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. If after the evaluation, the event is deemed unrelated to immunotherapy, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6 for dose modification.

Pneumonitis:

- For **Grade 2 events**, treat with systemic corticosteroids.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- When symptoms improve to Grade 1 or less, taper steroid over 4 or more weeks.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Infusion Reactions:

- Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Diarrhea/Colitis:

Carefully monitor for signs and symptoms of enterocolitis (e.g. diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (e.g. peritoneal signs and ileus).

- Advised all to drink liberal quantities of clear fluids. If oral fluid intake is insufficient, IV fluid and electrolytes supplementation is advised. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2** events, administer oral corticosteroids.
- For **Grade 3 or 4** events, treat with IV followed by high dose oral steroids.

When symptoms improve to Grade 1 or less, taper steroid over 4 or more weeks.

Hypophysitis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4**, treat initially with IV followed by oral corticosteroids.
- When symptoms improve to Grade 1 or less, taper steroid over 4 or more weeks.
- Replace hormones as warranted as the steroid dose is tapered

Type 1 diabetes mellitus [*if new onset, Grade ≥3 Hyperglycemia, associated with ketosis (ketonuria) or metabolic acidosis (DKA)]*

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate serum glucose, metabolic panel, glycosylated hemoglobin, and C-peptide as well as urine ketones.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) preferred.
  - In hypothyroidism, thyroid hormone replacement therapy with levothyroxine or liothyroinine as per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat initially with IV followed by oral corticosteroids. When symptoms improve to Grade 1 or less, taper steroid over 4 or more weeks.
  - Replace hormones as warranted as the steroid dose is tapered

Hepatic:

- For **Grade 2** events, monitor liver function tests more frequently (consider weekly) until returned to baseline. Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24-48 hours.
- When symptoms improve to Grade 1 or less, taper steroid over 4 or more weeks.

Immune-mediated myocarditis

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.
- Permanently discontinue the related immunotherapy for confirmed immune-mediated myocarditis.

Renal Failure or Nephritis:

- For **Grade 2** events, treat with oral corticosteroids.
- For **Grade 3-4** events, treat with IV or oral corticosteroids.
- When symptoms improve to Grade 1 or less, taper steroid over 4 or more weeks.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

- For signs or symptoms of SJS or TEN, withhold immunotherapy and refer the patient for specialized care for assessment and treatment.
- If SJS or TEN is confirmed, permanently discontinue the related immunotherapy.

Refer to Appendices E and F for Toxicity Management Algorithms for Nivolumab and Ipilimumab, respectively.

TREATMENT GUIDELINES FOR INFUSION REACTIONS		
NCI CTCAE Grade	**Treatment**	**Premedication for Next Dose**
Grade 1 Mild reaction; infusion interruption and intervention not indicated	Increase monitoring of vital signs as medically indicated until medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion and monitor** Additional therapy options: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping infusion, the infusion may be restarted at 50% of the original rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing held until symptoms resolve and premedication required for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should discontinue therapy.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500-1000 mg PO (or equivalent antipyretic
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to medication and/or brief interruption); recurrence of symptoms following initial improvement; hospitalization indicated for other sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional medical options: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until medically stable in the opinion of the investigator. Hospitalization may be indicated. **Permanently discontinue related immunotherapy**	**No subsequent dosing**
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.5.2 Diet/Activity/Other Considerations

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

5.6 Contraception

Nivolumab and ipilimumab have adverse effects on a fetus in utero and may have transient adverse effects on the composition of sperm.

Male subjects are considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying condition).

Female subjects are considered of non-reproductive potential if any below apply:

1. Congenital or acquired condition that prevents childbearing
2. Postmenopausal (12 or more months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
3. Status post hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, 6 or more weeks prior to start of treatment.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 5 months for female and 7 months for male subjects after the last dose of study drug by any of the following methods:

1. Abstinence from heterosexual activity
   ** Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.
2. Acceptable contraception during heterosexual activity by subject or partner
   - Single method (one of the following is acceptable):
     - intrauterine device (IUD)
     - vasectomy of a female subject's male partner
     - contraceptive rod implanted into the skin
   - Combination method (requires use of two of the following):
     - diaphragm with spermicide (NOT in conjunction with cervical cap/spermicide)
     - cervical cap with spermicide (nulliparous women only)
     - contraceptive sponge (nulliparous women only)
     - male condom or female condom (cannot be used together)
     - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

** If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 5 months for female and 7 months for male subjects after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study. Subjects should be informed that taking the study medication might involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

5.6.1 Pregnancy

If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to BMS within 2 working days if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to BMS.

5.6.2 Nursing Women

It is unknown whether nivolumab or ipilimumab are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or withdrawn from the trial at the discretion of the investigator for any untoward effect. A subject may also be withdrawn by the investigator or the Sponsor if enrollment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

5.8 Criteria for Taking a Participant off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Treatment will be discontinued for clinical or radiographic progression of disease, intolerance despite dose modification (defined as NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 Grade 3 or 4 that does not return to Grade 1 or 2 after interruption or reduction of dose for 4 weeks), or patient withdrawal. A patient who experiences a dose-limiting toxicity (DLT) can remain on study at a reduced dose, if deemed by the physician to be safe and beneficial for the patient to continue.

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

- Global deterioration of health-related symptoms (clinical progression),
- Confirmed radiographic disease progression,

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Treatment interruption for more than 4 consecutive weeks due to intolerance despite appropriate dose modification,
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator,
- Protocol non-compliance,
- Pregnancy,
- Lost to follow-up, or
- Study termination by Investigator, Institution or IRB.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that all unused investigational product(s) be returned, request the patient to return for a final visit, if applicable, and advise follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the trial and also withdraws consent for disclosure of future information, then no further evaluations should be performed and no additional data should be collected. The Investigator may retain and continue to use any data collected before such withdrawal of consent.

If the participant undergoes another surgery for presumed tumor progression but pathological findings are consistent with pseudoprogression (inflammation and necrosis rather than active tumor), the participant will deemed to not have had tumor progression and may continue treatment with nivolumab after review with the principal investigator.

5.9 Duration of Follow Up

After documented progression each subject will be followed by telephone or medical record review for survival until they meet criteria for removal from study as per below.

5.10 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following apply: lost to follow-up, withdrawal of consent, or death. The reason for taking a participant off study, and date the participant was removed, must be documented in the case report form (CRF).

Severe adverse events, availability of new adverse toxicology in animals, and financial difficulties due to withdrawal of funds may result in stopping the trial. The investigator or IRB may take such actions. If the trial is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-up will be available. If an investigator terminates the trial, the investigator will inform the subjects and IRB about the reason for such action. Similar notifications will be sent by the IRB if it takes such an action.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the clinical source documentation.

6. DOSING DELAYS/DOSE MODIFICATIONS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications for nivolumab and ipilimumab.

Patients with Grade 3-4 scalp skin toxicity from NovoTTF200A (Optune™) application, should hold TTFields therapy until resolved to Grade ≤2, then resume at same compliance goal of 75% or above. Interval maximal topical or systemic therapy advised. Repositioning of arrays is advised for any Grade ≤2 along with maximal medical therapy.

Adverse events (both non-serious and serious) associated with nivolumab and/or ipilimumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Immunotherapy must be withheld for drug-related toxicities and severe or life threatening toxicities. See Section 5.5.1 for supportive care guidelines, including use of corticosteroids.

Criteria for disrupting treatment, dose modification, or discontinuation for adverse events that are attributable to nivolumab or ipilimumab are listed below. After dose modifications are per the clinical judgment of the investigator and agreement of the subject, the treatment will be resumed according to the table below. Dose modification may not be required for adverse events that are clinically manageable.

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/ Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or High Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)	Permanently discontinue
Type 1 diabetes mellitus (new onset) or Hyperglycemia	T1DM or 3-4	Hold immunotherapy for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume immunotherapy when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with immunotherapy can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

Toxicity	Hold For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with immunotherapy can be continued while thyroid replacement therapy is instituted	Therapy with immunotherapy can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[a]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[b]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Investigator's Brochure (IB) – Infusion Treatment Guidelines for further management details.

[b] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose

If a patient experiences other adverse events, or several adverse events and there are conflicting recommendations based on Grade, the investigator will use the lowest reduced the dose. Dose modifications will be made based on an adverse event that occurs during any time during a cycle.

Participants who experience an adverse event that requires a treatment delay or dose reduction should be monitored with appropriate laboratory testing or other clinical evaluation at least weekly until resolution; if the adverse event does not resolve within 12 weeks, the Investigator will determine the best course of action.

For holds for reasons other than treatment related toxicities, if the participant does not meet criteria to resume treatment within 6 weeks of the event precipitating the hold, the study agent(s) may be restarted, as long as there has been no significant evidence of disease progression (e.g., by clinical findings, symptoms, tumor markers) during the treatment interruption.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An **Adverse Event (AE)** is defined as any untoward medical occurrence in any subject given a pharmaceutical or biomedical product and irrespective of a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (Example an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of any nivolumab or ipilimumab infusion or TTFields therapy is also an adverse event.
Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to onset of menses or menopause occurring at a physiologically appropriate time.

Adverse events may occur during the course of the clinical trial or within the follow-up period specified by the protocol, from overdose (whether accidental or intentional), from abuse and from withdrawal. Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event.

All adverse events will be recorded starting from the date of screening and at each examination through 100 days following cessation of treatment. Serious Adverse Events will be followed through 100 days following cessation of treatment. Both Adverse Events and Serious Adverse Events will not be collected for subjects until they have signed the informed consent form and undergone protocol-specified procedures or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

AE monitoring and reporting is a routine part of every clinical trial. All Adverse Events regardless of seriousness or relationship to the Investigational Product will be recorded in the Case Report Forms. Serious Adverse Events should be reported per the requirements described in Section 7.1.

7.1 Reporting of Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose or during any use trial therapies as defined in section 7.2. Progression of the cancer under study is not considered an adverse event.

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing for Nivoulmab/Ipilumumab must be reported to BMS Worldwide Safety, whether related or not related to study drugs. All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of NovoTTF200A (Optune™) and/or last dose of any infusion, whether related or not related to study device or agents will be collected and reported. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug or device, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

If the BMS safety address is not included in the protocol document (e.g., multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. The BMS protocol ID number must be included on the form submitted by the Sponsor/Investigator.

BMS Contact:	Worldwide.Safety@bms.com and aepbusinessprocess@bms.com
Novocure Contact:	Support@novocure.com
CIOMS Form:	http://www.cioms.ch/index.php/cioms-form-i
MedWatch Form:	https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of events will be in the form of a SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered

associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

- Canada Phase IV AE reporting requirement:
  - The Division 8 of the Food and Drug Regulations in Canada require that any cases of Unusual Failure in Efficacy occurring in Canada be reported to the Canadian Health Authorities in an expedited manner.
  - Canadian sites will record single cases of Unusual Failure in Efficacy as an Adverse Event. This reporting requirement is specific for Canadian sites only.
    - ✓ This AE is required to be reported to BMS within 24 hours by the Investigator/site staff becoming aware of the report
    - ✓ For transmission purposes, report this AE using the paper SAE form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS and Novocure within 24 hours. For BMS, SAEs must be recorded on either CIOMS or MedWatch form and pregnancies must be reported on a Pregnancy Surveillance Form or can be submitted on the aforementioned SAE form to BMS.

- SAE Email Address: Worldwide.Safety@BMS.com
- SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Bristol-Myers Squibb, Inc., Novocure, Inc., and Miami Cancer Institute will submit all required SAE Reports and Annual Progress Reports to the FDA as required by FDA or other local regulators. [1 SEP] Investigators must report to Bristol-Myers Squibb, Inc. and Novocure, Inc. any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last treatment on the local institutional SAE form. An FDA Form 3500A (MedWatch) or the local institutional SAE form may be used.

Investigators must report SAEs to the local IRB following local IRB reporting requirements.

7.2 Definition of Serious Adverse Events

SERIOUS ADVERSE EVENTS
A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose or during any use trial therapies that:

- Results in death,
- Is life threatening, (defined as an event in which the participant was 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)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- Results in persistent or significant disability/incapacity,
- Results in or prolongs an existing inpatient hospitalization,
- Is a congenital anomaly/birth defect,
- Is a new cancer (that is not a condition of the study),
- Is associated with an overdose,
- Is another important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE regarding hospitalizations: The PI determines if information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- Visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

Progression of the cancer under study is not considered an adverse event.

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Definite:	The AE is clearly related to the study treatment.
Probable:	The AE is likely related to the study treatment.
Possible:	The AE may be related to the study treatment.
Unlikely:	The AE is doubtfully related to the study treatment.
Unrelated:	The AE is clearly NOT related to the study treatment.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A non-serious adverse event is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such. The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.
Wherever possible, timely confirmation of initial liver related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:
1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Pregnancy
If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations
Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE,

as appropriate, and reported accordingly.

7.3 Expected Toxicities

Refer to the Investigator's Brochure (IB) for detailed toxicity information. Refer to sections 2.2.3, 2.4.5 and 2.5.4 for summaries for Optune™ (NovoTTF200A), Opdivo™ (nivolumab), and Yervoy™ (ipilimumab), respectively.

7.4 Adverse Event Characteristics

CTCAE term (AE description) and grade:
The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE:

Definite:	The AE is clearly related to the study treatment.
Probable:	The AE is likely related to the study treatment.
Possible:	The AE may be related to the study treatment.
Unlikely:	The AE is doubtfully related to the study treatment.
Unrelated:	The AE is clearly NOT related to the study treatment.

8. PHARMACEUTICAL INFORMATION

Refer to the Investigator's Brochure (IB) and Lab Manual for detailed information.

8.1 Product Supply, Administration and Inventory

8.1.1 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.2 Availability

Bristol-Myers Squibb (BMS), Inc. will provide nivolumab (Opdivo™) and ipilimumab (Yervoy™). BMS will provide Nivolumab in 100 mg vials, 10mg/mL. BMS will provide Ipilimumab in 200 mg vials, 5 mg/mL.
Novocure, Inc. will provide the NovoTTF200A (Optune™) device once insurance approved and as per standard practice.

8.1.3 Administration

Refer to the Investigator's Brochure (IB) and Lab Manual for detailed information regarding drug and device administration.

The infusions of nivolumab and ipilimumab will each be infused over 30 minutes in the same way as in the CHECKMATE-142 (NCT02060188) study. On days that nivolumab and ipilimumab are both administered, the nivolumab is given first in sequence.

8.1.4 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful

record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

8.1.5 Destruction and Return

Unused supplies of nivolumab or ipilimumab will be destroyed on-site according to local practices within 60 days of completion of the study, after accountability has been completed.

Unused arrays and all NovoTTF200A (Optune™) device components will be returned to Novocure, Inc. at the end of TTFields therapy while on or after trial as per standard practice.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Analyses

Correlative assays will be performed on archival tissue to measure biomarkers of therapeutic response, including MGMT, PD1/PDL1 expression, mutational load, etc., as funding permits. Collection and processing procedures as well as supplies needed are detailed in the Laboratory Manual associated with this protocol.

Archival tumor assessments of immune regulation will be performed on tissue obtained from participants. If available, a minimum of one (1) formalin-fixed paraffin-embedded (FFPE) archival tumor tissue block (preferred) or a minimum of 4 FFPE unstained sections from most recent pre-registration biopsy/surgery are to be submitted within 60 days of registration. Please refer to the study Laboratory Manual for shipping instructions.

10. STUDY CALENDAR

Study visits and procedures have ±2 day scheduling window, except for Screening visit and neuroimaging (contrast-enhanced CT or MRI) that have a ±7 day window. A treatment cycle is defined as 6 weeks with 3 treatments of Nivolumab and 1 treatment of Ipilimumab (Arm B only).**Schedule of Assessments**

Footnotes:

*** For Cortisol, TSH/free T4, and ACTH, baseline lab results suffice to clear for C1D1 and any cycle X W1, W3, W5 results suffice to clear for next infusion on W3, W5, and cycle X+1 W1, respectively.**

1. Abbreviated Physical Exam on Day 1 of each Treatment Cycle
2. Neurological assessments will use the NANO scale
3. Vital signs: Vital signs: systolic and diastolic blood pressure, respiration, pulse, oral temperature prior to each infusion
4. Determine if significant weight loss or gain (±10%) prior to every infusion
5. Hematologic lab values should be re-evaluated on cycle 1 day 1 and need to meet eligibility parameters to start treatment
6. Pregnancy tests (minimum sensitivity 25 IU/L or equivalent units of HCG) are required for women with childbearing potential, defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., menses at any time in the preceding 24 consecutive months).
7. Every 2-3 months, via telephone, for all subjects for a minimum of 1 year, or indefinitely until death or loss to follow-up
8. Obtain archival tumor tissue (if available) at enrollment, in accordance with the Laboratory Manual..

Schedule of Assessments						
Study Visits/ Windows	**Screening/ Baseline**	**Treatment Cycles**		**Observation**	**End of Treatment**	**Follow-Up**
Procedures	Within 14 days of Treatment	C__W1	C__W3, W5	After max therapy or toxicity discontinuation	30 (±3 days) after last dose	Every 2-3 months
		Every 6 weeks (±7 days)	(±2 days)	Every 8 weeks (±7 days)		
Informed Consent	x			.		
Medical/Rx History	x	x	x	x	x	
Physical exam[1], Neurologic Exam[2], KPS	x	x	x	x	x	
Vital signs[3], Weight[4]	x	x	x	x	x	
Height	x					
Hematology[5]	*Screening/ Baseline*: within 14 days prior to first infusion *Treatment Cycles*: within 2 days prior to each infusion *Observation*: every 8 weeks with each clinical and/or CT/MRI assessment				x	
Full Serum Chemistry					x	
AM Cortisol Testing*	x	x	x			
TSH, free T4*	x	x	x		x	
ACTH*	x	x	x		x	
PT, PTT, INR*	*Screening/ Baseline*: within 24 hours of start of treatment *Treatment Cycles*: every 6 weeks while on immunotherapy				x	
Urinalysis					x	
Pregnancy Test[6]					x	
FACT-BR Questionnaire	x	x		x	x	
NovoTTF200A (OptuneTM)[7]		x	x			
Nivolumab		x	x			
Ipilimumab (Arm B Only)		x				
MRI or CT Scan	*Screening/ Baseline*: Within 14 days of Treatment *Treatment Cycles*: Every 6 weeks (within 7 days prior to treatment) *Observation*: Every 8 weeks Every 8 weeks (±7 days)				x	
AE/ SAE	AEs are recorded from the date of initiation of therapy and at each examination until 30 days after last dose of Nivolumab. SAEs will be followed through 100 days after last dose of Nivolumab.					
Con-meds	x	x	x	x	x	
Disease Status and Survival[8]						x
Archival Tumor Tissue[9]	x					

11. MEASUREMENT OF EFFECT

After signing informed consent patients will undergo screening procedures including baseline radiologic imaging by contrast-enhanced CT or MRI within 14 days prior to starting therapy. Patients who remain on study will have tumor assessments performed every 6 weeks while on a maximum of 24 months of therapy, thereafter every 8 weeks while off therapy (Observation period). In addition to reassessment scans, confirmatory scans should also be obtained at ≥4 weeks following initial documentation of objective response. To be assigned a status of PR or CR changes in tumor measurements must be confirmed by repeat assessments that should be performed at ≥4 weeks after the criteria for response are first met.

Response will be assessed by the modified immune Revised Assessment in Neuro-Oncology (iRANO) response criteria.

11.1 Definitions

Evaluable for Objective Response
Only those patients with measurable disease present at baseline will be enrolled on study.

Only patients who received at least one cycle (6 weeks) of therapy and response assessment with brain MRI or CT at least 6 weeks from the first dose will be considered evaluable for overall survival or disease progression. Patients who discontinue therapy for reasons other than progression prior to response assessment will not be evaluable for survival and will be replaced.

Only patients with measurable disease present at baseline, completing at least one cycle (6 weeks) of therapy, and disease re-evaluated radiographically will be considered evaluable for partial or complete response.

Any patient who initiates treatment and is later found to be ineligible for study (e.g., protocol violation) will be withdrawn from study but will be followed for disease progression, toxicity and survival. The experience of such patients will be characterized separately from that of evaluable patients. Reasons for exclusion of enrolled patients from the analysis set for efficacy, or for safety, will be characterized.

Evaluable Non-Target Disease Response
Patients with lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle (6 weeks) of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression.

All patients who have received at least one dose infusion of nivolumab and/or initiate TTFields therapy are evaluable for safety and toxicity.

Disease Parameters
For the purposes of this study, patients will be evaluated for response approximately every 6 weeks of therapy starting from the first dose for the initial 24 months, thereafter approximately every 8 weeks. In addition to baseline scans, confirmatory scans will be obtained at ≥4 weeks following initial documentation of objective response or disease progression.

11.2 Disease Parameters

Measurable Disease
Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices (≥5 mm apart with 0 mm skip). Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Non-Measurable Evaluable Disease
Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter <1cm.

11.3 Response/Progression Categories

The RANO Response Criteria will be used in this study as summarized below.

11.3.1 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 8 weeks. In the absence of a confirming scan at least 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. Participants must be on no steroids or on physiologic replacement doses only.
e. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.
f. Stable or improved non-enhancing (T2/FLAIR) lesions.

Non-measurable disease cannot have a complete response.

11.3.2 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 8 weeks. In the absence of a confirming scan at least 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.

Non-measurable disease cannot have a partial response.

11.3.3 Progressive disease (PD)

Any of the following criterions 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 and sustained for at least 8 weeks. In the absence of a confirming scan at least 4 weeks later, this scan will be considered only stable disease.

b. Any new enhancing measurable 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 it is recommended that 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, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
d. Failure to return for evaluation due to death or deteriorating condition.

11.3.4 **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.

11.3.5 **Unknown response status**

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

11.4 Methods for Evaluation of Disease

All measurements must be performed and recorded in metric notation using ruler, calipers, or digital measurement tools. All baseline measurement should be performed as close to initiation of treatment and never >4 weeks before the treatment.

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

11.5 Evaluation of Best Response

The best overall response is the best response recorded from the treatment start until disease progression (using 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. Participants without measurable disease may only achieve SD or PD as their best “response.”

12. DATA REPORTING / REGULATORY REQUIREMENTS

Lists, guidelines, and instructions for reporting adverse events are listed in Section 7.

12.1 Data Reporting

Investigative sites are responsible for completing and submitting data and/or data forms according to the user requirements.

12.2 Data Collection

12.2.1 Data Collection Forms

The Miami Cancer Institute (MCI) Clinical Trial Office (CTO) will be responsible for all data management.

Case Report Forms will be generated by the CTO. Case Report Forms will be completed in a timely manner by the respective site. The trial will use a web-based Electronic Data Capture (EDC) system for all data collection. Case Report Form completion may be formally delegated to other study personnel listed in the delegation of authority (DOA) form and signed by the PI or co-investigator.

The following steps will ensure accurate, consistent, complete and reliable data:

1. The Investigator/Institution will conduct an initiation meeting at the study site prior to the start of the study. The study protocol, procedures and CRFs will be reviewed in detail and the study personnel will be trained to carry out the procedures defined in the protocol.
2. The Investigator will maintain a Study Site Binder for storing study related regulatory and study site documentation: study logs and forms.
3. All written study documentation entries must be made in blue or black ink. The investigator must review all entries for completeness and accuracy. When changes or corrections are made on any study documentation, the person making the change must draw a single line through the error, then initial and date the correction.
4. Periodic monitoring by the MCI CTO data management team will verify the accuracy of data entered on each CRF against the raw data from source documents at the site. Items needing correction/clarification will be identified and brought to the attention of the study site personnel and Principal Investigator, and corrections will be made as appropriate.
5. Once the Investigator/Institution performs a final review of the CRF, study database will be validated using appropriate validation processes.

12.2.2 Registration and Eligibility

The investigator will confirm patient eligibility. The investigator is responsible for enrolling only those patients who meet protocol eligibility criteria.

12.2.3 Data Safety and Monitoring Board (DSMB)

Miami Cancer Institute DSMB will provide trial oversight per the Data Safety Monitoring Plan (DSMP).

12.3 Regulatory Requirements

12.3.1 Patient Consent Form

Informed consent must be obtained before protocol-specified procedures or interventions are carried out. The investigator will explain the nature of the study and will inform the subject that participation is voluntary and that they can withdraw at any time. A copy of the signed consent form will be given to every participant and the original will be maintained with the subject's records.

The consent form must be approved by the IRB. Consent forms are written to be understood by prospective subjects. The Informed Consent should be translated and certified into the local language of the respondent, as deemed necessary. Informed consent will be documented by the use of a written consent form approved by the IRB and signed and dated by the subject and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities. The subject should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

12.3.2 Site Monitoring

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, and duly authorized representative of any entity providing support for this trial. Routine monitoring or audit activities for this study should be conducted by appropriately authorized personnel as warranted. The general scope of such visits would be to inspect study data (regulatory requirements), source documentation and CRF completion in accordance with current FDA Good Clinical Practices (GCP), the ICH guidelines and the respective local and national government regulations and guidelines.

12.3.3 Institutional Review Board Approval

This protocol, the informed consent document, relevant supporting information and all types of patient recruitment and advertisement information must be submitted to the local IRB for review and must be approved before the study is initiated. An amendment to remove a life-threatening situation can by implemented by the Investigator prior to obtaining IRB approval by the site. In such situations, the IRB must be notified immediately and the amendment forwarded to the IRB for their consideration.

The investigator is responsible for keeping the local IRB informed of the progress with study renewal at least once a year. The investigator must also keep the local IRB informed of any significant adverse events, per local institutional guidelines.

12.3.4 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all study-related documentation, including source document and CRFs for:

- Two years after the FDA approved the marketing application, or
- Two years after the FDA disapproves the application for the indication being studied, or
- Two years after the FDA is notified of the discontinuation of the trial, and that an application will not be submitted.

For all studies, including studies with FDA-IND exemption, the Investigator/ Institution will take measures to prevent accidental or premature destruction of study documents. For such studies conducted under IND exemption, records will be retained for a minimum of seven (7) years past official study termination. Sponsored trials should be contacted upon the study team becoming aware of the relocation of study documents or prior to destroying any study documents.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design and Sample Size

We propose an open label, two parallel arm, two-stage, phase II trial to determine the efficacy, in terms of objective response rate (ORR), of combination therapy with tumor treating fields (TTFields) therapy, nivolumab with or without ipilimumab in adult patients with bevacizumab-naïve, recurrent glioblastoma. Best objective response rate (ORR) is defined as the proportion of evaluable patients who achieve complete (CR) or partial response (PR) according to modified immunotherapy iRANO criteria. Secondary objectives include safety, ORR by standard RANO criteria, overall survival (OS), progression-free survival (PFS), clinical benefit (defined as ORR plus stable disease >12 weeks), compliance rates of TTFields therapy at or above goal of 75%, and exploratory correlations between response or survival and compliance rates, serum and/or tumor tissue biomarkers. Primary analyses are performed for each arm, but secondarily assessed for the entire cohort as well.

The EF-11 study showed a response rate of 14% among patients with recurrent glioblastomas treated with TTFields alone compared to physician's choice medical therapy (Stupp et al, Eur J Cancer 2012). Thus, the null H0 is set at 14% and H1 (target ORR) set at 35% for each arm. Power is set at 85% with a 1-sided alpha of 0.05.

If no response is seen after 15 eligible patients are accrued in either arm, that arm will close for futility. Based on a MiniMax design, if >2 responses are seen on the first 15 patients in either arm, then 15 more patients will be accrued in the arm. If ≥7 responses are seen among the 30 patients in either arm, this regimen deserves further investigation. Sample size will be 30 maximum per cohort/arm for a total of 30 to 60 subjects enrolled on study.

13.2 Definitions

Evaluable: All study-eligible patients who receive at least one infusion of nivolumab will be considered *evaluable for safety and toxicity*. To be *evaluable for efficacy*, patients must be study eligible, receive at least one cycle (6 weeks) of immunotherapy and complete initial disease assessment at ≥ 6 weeks after starting therapy.

Exclusions: Any patient who is enrolled on study, but does not receive any component of study treatment, will be excluded from all efficacy analyses. Any patient who initiates treatment and is later found to be ineligible for study (e.g., protocol violation) will be withdrawn from study but will be followed for disease progression, toxicity and survival. The experience of such patients will be characterized separately from that of evaluable patients. Reasons for exclusion of enrolled patients from the analysis set for efficacy, or for safety, will be characterized.

Overall response rate (ORR): Overall response rate is the proportion of patients whose best overall response per modified iRANO criteria or standard RANO criteria is complete (CR) or partial (PR) after at least 6 weeks from start of therapy. iRANO additionally requires best overall response of CR or PR to be sustained, that is, confirmed by a second assessment at ≥ 4 weeks later. Patients who clinically progress before the initial radiographic assessment after 1 cycle (6 weeks) will be considered nonresponders.

Progression-free survival (PFS): PFS will be measured from the start date of treatment until

documented evidence of disease progression, clinical progression or death from any cause, after at least 8 weeks from start of therapy. Radiographic progression should be confirmed by a second assessment at ≥4 weeks later. For patients who remain alive without progression, follow up time will be censored at the date of last assessment.

Overall survival (OS): Survival will be measured from the start date of treatment to the date of death from any cause or last contact (censored observations).

13.3 Enrollment and Study Duration

We expect to enroll at an average rate of two patients per month and complete accrual within two years. Patients will be followed for a minimum of one additional year. Thus study duration is expected to be approximately three years.

13.4 Statistical Analyses

Baseline characteristics will be summarized using descriptive statistics: count, percentage, range, median, mean, and standard deviation as appropriate. Data include demographics (age, sex, race/ethnicity), performance status, laboratory parameters and prior therapy.

Treatment duration will be summarized by the number of immunotherapy cycles (6 weeks each). Frequency and reason for dose modifications and discontinuation of any therapy will be detailed.

We will report the objective response rate with corresponding two-side 90% confidence interval (CI) using the exact binomial method (Armitage et al, 2002). We will also report the objective response rate, the median and range for time to response, and duration of CR or PR. Time to progression will be summarized by the median and range for patients whose best response is SD as well as for all patients who develop progressive disease.

The Kaplan-Meier method will be used to estimate progression-free and overall survival. Point estimates for the proportion of progression-free and surviving patients will be given for selected times, specifically 6 and 12 months, along with corresponding 95% confidence intervals using the log-log transformed method and Greenwood's variance. To the extent possible with 30-60 study patients, we will investigate the relationship between tissue and serum biomarkers and overall response using logistic regression. Similarly, biomarker associations with progression free and overall survival will be explored using the log rank test and Cox regression.

Safety will be assessed by tabulating toxicities according to type, grade, duration, and attribution to study treatment in accordance with *NCI Common Terminology Criteria for Adverse Events* (CTCAE version 4.0). We will also report the distribution of worst grade toxicity in study patients.

TTFields compliance data is collect during monthly in-home visits by Novocure representative in order to assess NovoTTF200A (Optune™) function and address patient concerns. The compliance rates are an average (mean ± stdev) over the 28-31 days of the month and provided in graphical and numerical form. Appendix D shows sample compliance reports with weighted average (mean ± stdev) per month. These data are provided as part of standard of care and included in the patient medical record. The weighted average will be compared to ORR, OS and PFS using the appropriate logistic or Cox regression models.

Quality of life will be assessed using the NRG/RTOG tool Functional Assessment of Cancer

Therapy-Brain (FACT-Br). FACT-Br is a validated tool measuring general quality of life (QOL) that assesses symptoms or problems associated with CNS tumors across 5 scales (Cella DF, 1993; Weitzner MA, 1995). FACT-Br yields data about total QOL, as well as dimensions of disease specific physical, social/family, emotional, and functional well-being. The FACT-Br is written at the 4th grade reading level. Patients can complete it in 5-10 minutes. The self-report of quality of life can be completed by the patient or with the assistance of the examiner and does not require pre-certification.

Analysis of QOL will focus on the 33-item FACT-G score and the 20-item brain subscale, FACT-BR. Scores will be calculated in accordance with FACIT scoring guidelines (www.facit.org). Descriptive summaries of FACT-G and FACT-BR at baseline and at each planned follow-up will include median and range, means and standard deviations as well as graphical depiction. To the extent that a clinically meaningful difference can be established, we will also categorize changes from baseline as indicating improvement, worsening, or no change and summarize these by counts and percentages.

13.5 Interim Monitoring

The study team will continuously monitor study accruals, toxicities and clinical outcome. Early stopping for futility will be considered after 15 patients have been enrolled and treated in each arm. Using a Minimax design, the chance of early stoppage under the null is calculated at 65%. The median time to response for nivolumab is 2 months. Once subject 15 is enrolled for each arm, we will wait a minimum of 8 (median time to response) and maximum of 12 weeks (2 MRI cycles) to assess response if an objective response by iRANO has not been noted in the already accrued patients.

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APPENDIX A
Karnofsky Performance Status (KPS) Criteria

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B
Neurologic Assessment 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. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Study #, Participant # and Initials: _____ _____/_____
Date Assessment Performed (day/month/year): _____
Study time point (i.e. cycle 1, day 1, etc.): _____
Assessment performed by (please print name): _____

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 attempts

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

Study #, Participant # and Initials: _____ _____
Date Assessment Performed (day/month/year): _____
Study time point (i.e. cycle 1, day 1, etc.): _____
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 paraphrasic 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 alteration

APPENDIX C
Functional Assessment of Cancer Therapy-Brain 4.0 (FACT-Br)

FACT-Br (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

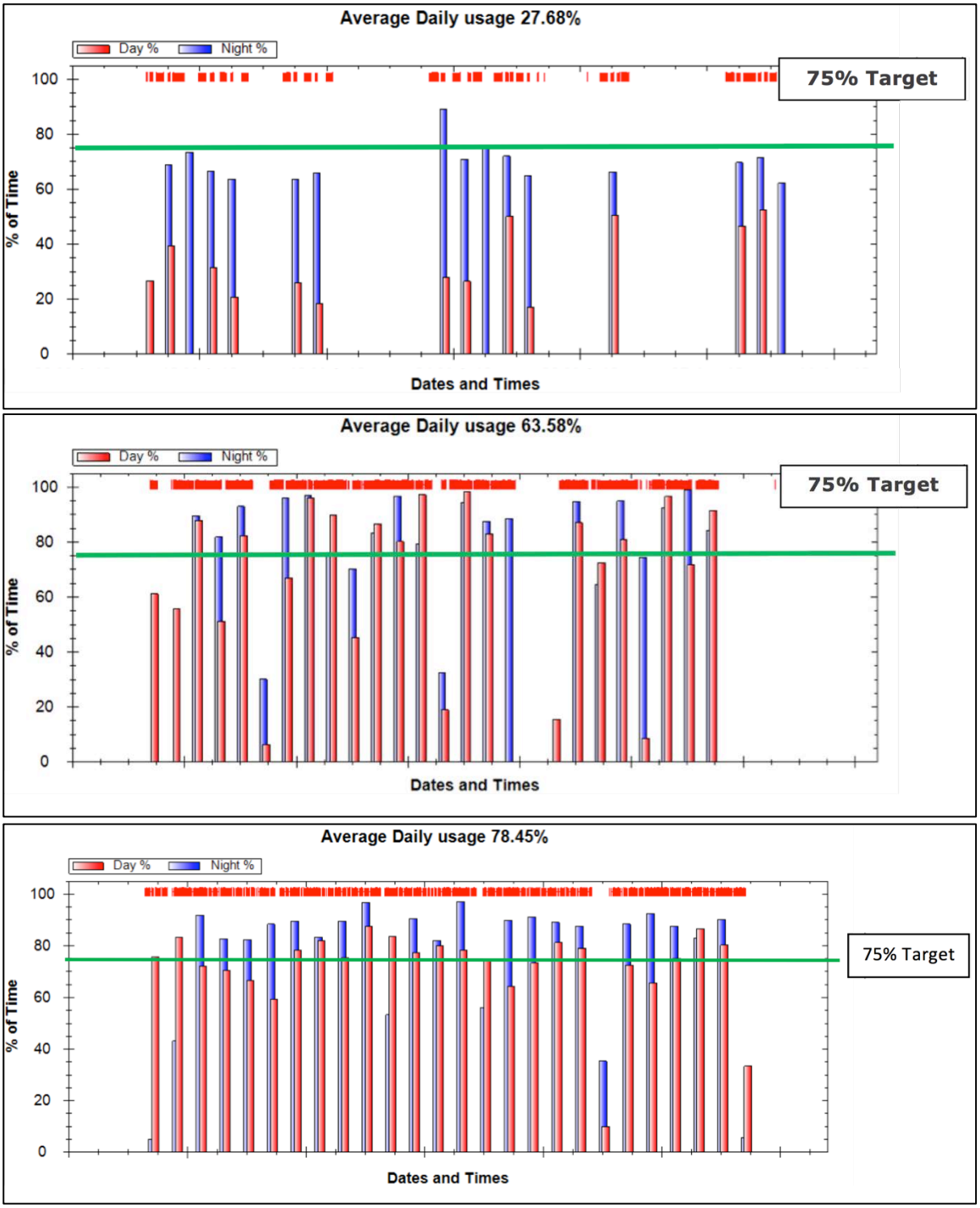
	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4

Refer to: www.facit.org

APPENDIX D

TTFields Compliance Reports Generated by NovoTTF200A (Optune™)

Panels show example graphs of compliance: Top = Low compliance; Middle = Compliance near goal; Bottom = Compliance above goal of 75%. The report also includes the number of days included, which allows calculation of weighted averages across the duration of TTFields therapy.



APPENDIX E
Toxicity Management Algorithms for Nivolumab
(Appendix 3 of Investigator Brochure BMS-936558/MDX1106/ONO-4538)

Appendix 3: Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Investigator Brochure
BMS-936558/MDX1106/ONO-4538 nivolumab

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

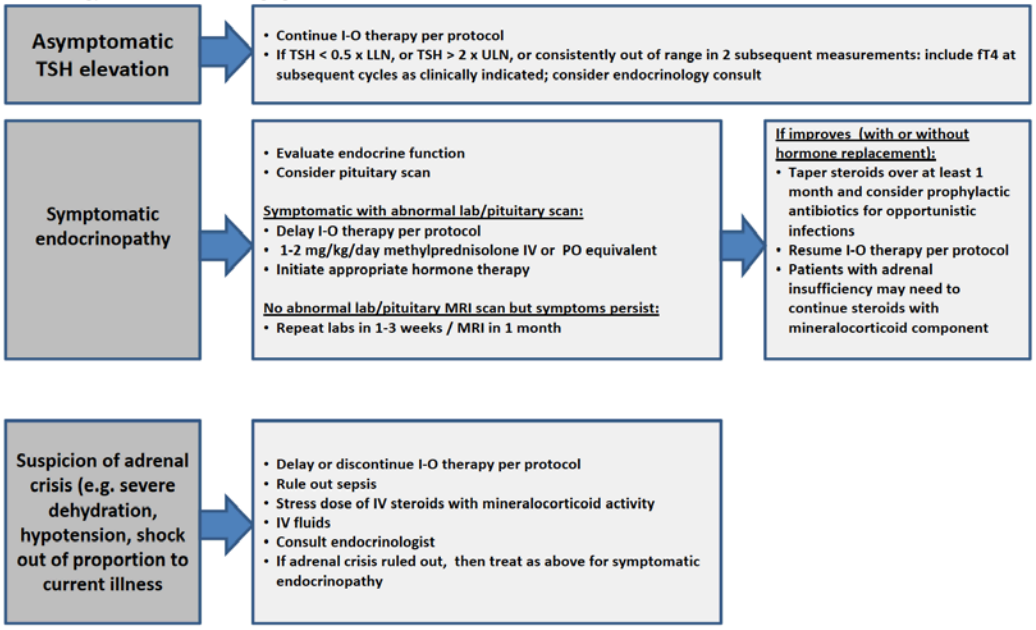
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

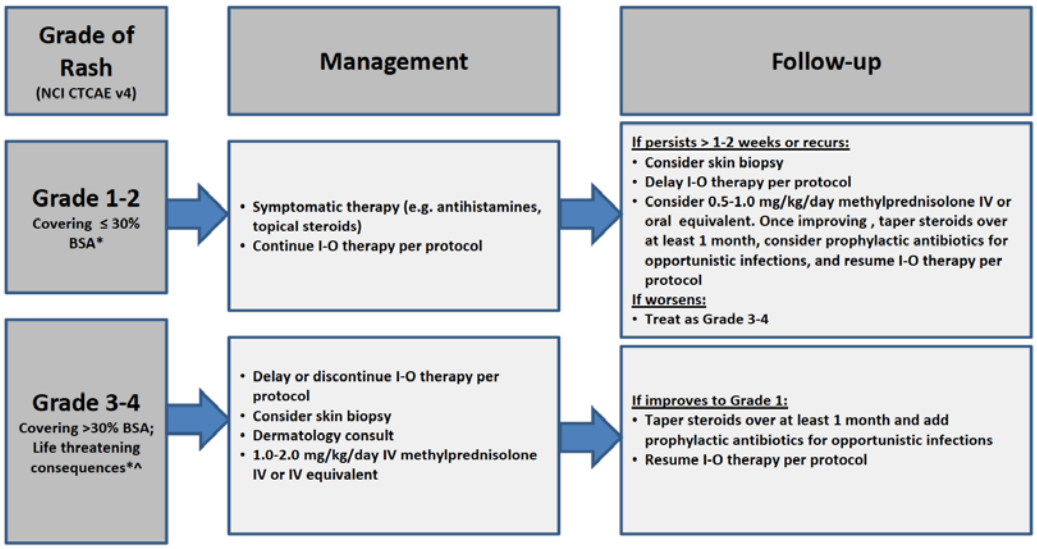
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

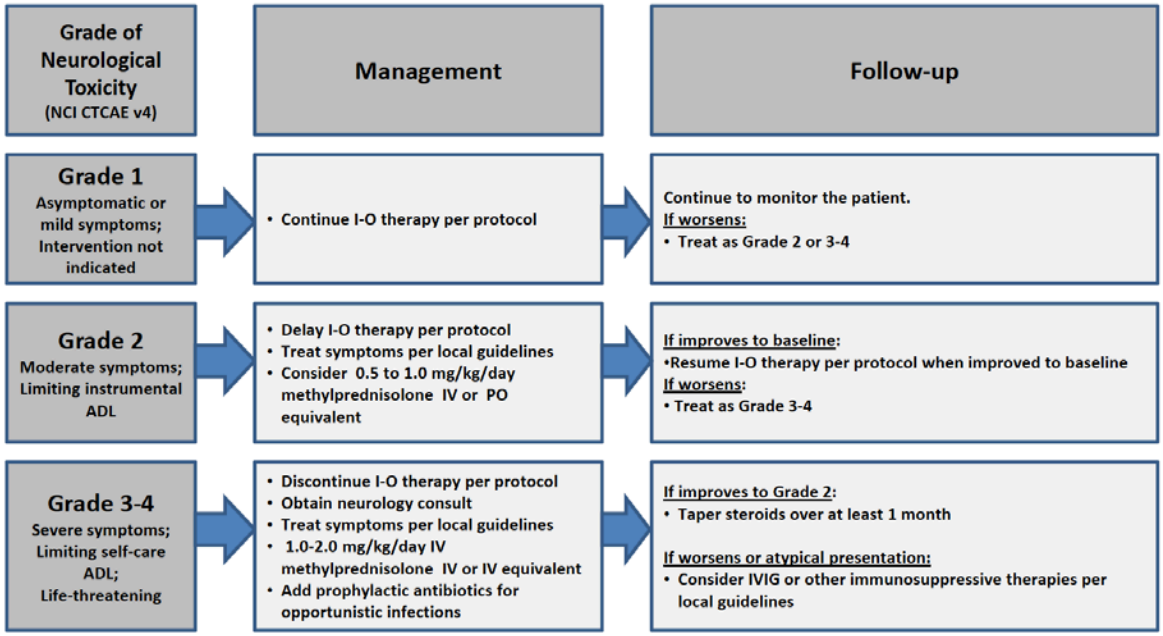
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX F
Toxicity Management Algorithms for Ipilimumab
(Appendix 3 of Investigator Brochure BMS-734016/MDX-010)

GI Toxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.
Opiates/narcotics mask symptoms of perforation! Infliximab should not be used in case of perforation/sepsis!

Severity of diarrhea/ colitis	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue ipilimumab • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report any worsening immediately
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Withhold/delay ipilimumab • Symptomatic treatment	**Symptoms improve/resolve** (grade 0/1): Resume ipilimumab **Symptoms persist for > 5-7 days, worsen, or recur:** • Moderate to high dose steroids PO (e.g., prednisone 0.5 - 1 mg/kg/day) • Continue to hold/delay ipilimumab until grade 1 • When symptoms are grade 1 or less slowly taper steroids over at least 1 month and resume ipilimumab. **Symptoms worsen:** Treat as grade 3/4
Grade 3-4 Diarrhea (G3*): ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs;interfering with ADL Colitis (G3*): fever, ileus, peritoneal signs	• Permanently discontinue ipilimumab • High dose IV steroids (e.g., methylprednisolone 1-2 mg/kg/day) • Consider endoscopy	**Symptoms improve:** • Continue steroids (same dose) until grade 1 • Then taper over at least 1 month **Symptoms persist 3-5 days, or recur after improvement:** • 1 dose* of infliximab 5 mg/kg (if no contraindication)

*G4 = life-threatening, perforation

*Some patients have required a second dose of infliximab

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

Hepatotoxicity Management Algorithm

Severity of hepatitis	Management	Follow-up
Grade 1 AST or ALT ≤ 2.5 x ULN or Total bilirubin ≤ 1.5 x ULN	• Continue ipilimumab	• Continue monitoring LFT prior to each dose
Grade 2 AST or ALT > 2.5 to ≤ 5.0 x ULN **or** Total bilirubin > 1.5 to ≤ 3.0 x ULN	• Increase frequency of monitoring (q3d) • Withhold/delay ipilimumab while investigating alternative etiology	**Return to baseline** • Resume q3w monitoring • Resume ipilimumab **Elevations persist for > 5-7 days or worsen, and no alternative etiologies are identified** • Consider moderate to high dose steroids PO (e.g., 0.5- 1 mg/kg/day prednisone or equivalent)
Grade 3-4 AST or ALT > 5.0 x ULN **or** Total bilirubin > 3.0 ULN	• Discontinue ipilimumab* • Increase frequency of monitoring (q1-3d) • High dose IV steroids (e.g., methylprednisolone 1-2 mg/kg/day**)	**AST/ALT/Tbili return to grade 2** • Taper steroids over at least 1 month **Labs do not decrease over 3-5 days, worsen or rebound:** • Add MMF*** 1 g BID • If no response within 3-5 days, consider other immunosuppressants per local guidelines

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

Caution: Infliximab is contraindicated in hepatic insufficiency!

*Ipilimumab may be held/delayed rather than discontinued if AST/ALT ≤ 8 x ULN and Tbili ≤ 5 x ULN. Resume ipilimumab when AST/ALT/ Tbili return to grade 2 and meet protocol specific retreatment criteria.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.
*** MMF, mycophenolate mofetil

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

Investigator Brochure
BMS-734016/MDX-010 Ipilimumab

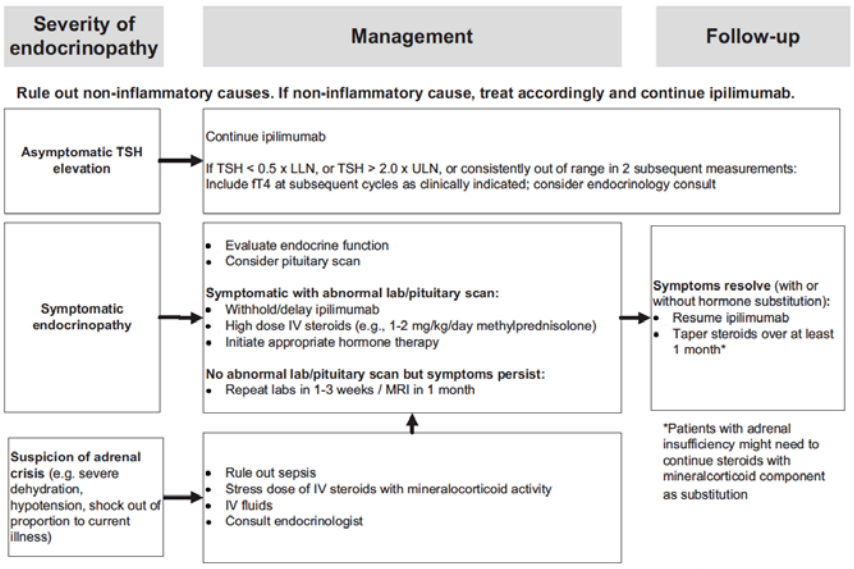
Skin Toxicity Management Algorithm

Severity of skin toxicity	Management	Follow-up
Grade 1-2	• Symptomatic therapy, e.g. antihistamines, topical steroids • Continue ipilimumab	**Symptoms resolve:** Continue ipilimumab **Symptoms persist > 1-2 weeks or recur:** • Continue ipilimumab • Moderate to high dose steroids PO (e.g., prednisone 0.5 - 1 mg/kg/day) • Once controlled, taper steroids over at least 1 month
Grade 3-4	• Hold/delay ipilimumab (regardless of relationship) • Take photos of rash • Consider skin biopsy • Dermatology consult • High dose IV steroids (e.g., methylprednisolone 1-2 mg/kg/day)	**Symptoms resolve / return to grade 1:** • Taper steroids over at least 1 month • Resume ipilimumab • Discontinue if grade 4 toxicity considered related

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

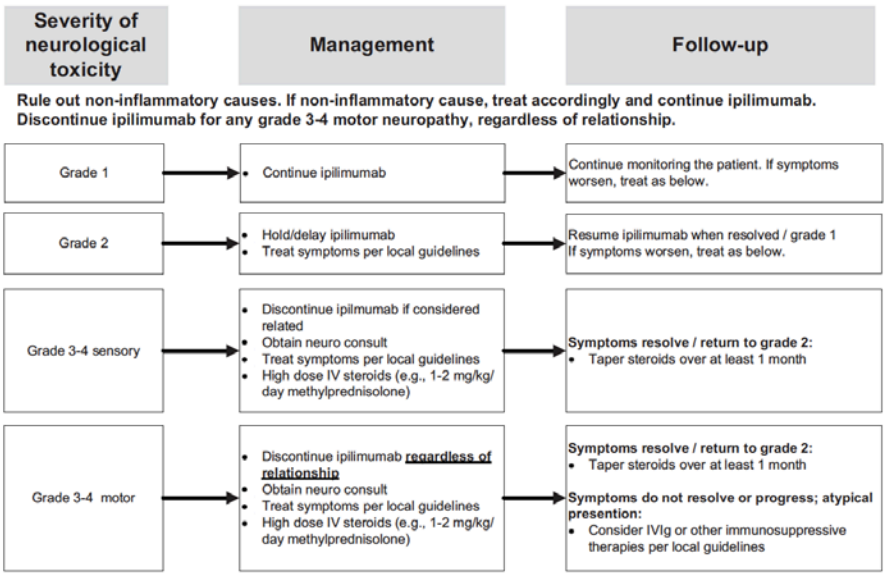
Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

Endocrinopathy Management Algorithm



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

Neurological Toxicity Management Algorithm



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.