

**A phase II, open-label, single arm, multicenter study of Avelumab with hypofractionated re-irradiation in adult subjects with transformed *IDH* mutant glioblastoma**

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**Funding Sponsor:** EMD Serono/Merck KGaA

**Study Product:** Avelumab (MSB0010718C)

**NYU Protocol Number:** s16-01179

**NCT Number:** NCT02968940

**IND Number:** 132960

**EMD Serono Study Number:** MS100070-0077

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**Initial version:** 12/28/2016  
**Amendment 1:** 1/26/2017  
**Amendment 2:** 3/14/2017  
**Amendment 3:** 4/24/2017  
**Amendment 4:** 7/11/2017  
**Amendment 5:** 1/13/2018  
**Amendment 6:** 10/30/2018

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## List of Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BID	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed-Tomography
CTL	Cytotoxic T cell
CTO	Clinical Trials Office
CXR	Chest X-ray
DLT	Dose Limiting Toxicity
DR	Duration of Response
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FISH	Fluorescence in situ Hybridization
GBM	Glioblastoma
GCPs	Good Clinical Practices
Gy	Gray (unit)
H <sub>1</sub>	Histamine H <sub>1</sub> receptor
HCT	Hematocrit
HFRT	Hypofractionated radiotherapy
HGB	Hemoglobin
HGG	High-grade glioma
HR	Hazard Ratio
IB	Investigator's Brochure
IC <sub>50</sub>	Concentration of 50% Inhibition
ICH	International Conference on Harmonization
IDH	Isocitrate dehydrogenase
IEC	Independent Ethics Committee
irAEs	Immune-related adverse events
IRB	Institutional Review Board
KPS	Karnofsky Performance Status
LGG	Low-grade glioma
LLN	Lower Limit of Normal
mAb	Monoclonal Antibody
MDSC	Myeloid-derived suppressor cell
MG	Malignant Glioma
MHC	Major histocompatibility complex

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MMR	Mismatch repair
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03
NSCLC	Non-small cell lung cancer
NYULMC	New York University Langone Medical Center
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral blood mononuclear cells
PCC	Perlmutter Cancer Center
PCV	Procarbazine, lomustine (CCNU), vincristine chemotherapy regimen
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PD	Pharmacodynamic
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS6	6-month progression-free survival
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
PTV	Planning Target Volume
QD	Once Daily
iRANO	Immunotherapy Response Assessment for Neuro-Oncology
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RT	Radiation Treatment
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic-Oxaloacetic Transaminase (also known as AST)
SGPT	Serum Glutamic-Pyruvic Transaminase (also known as ALT)
T <sub>1/2</sub>	Half-Life of the Terminal Disposition Rate Constant
TCR	T cell receptor
TIL	Tumor-infiltrating lymphocytes
TO	Target Occupancy
T <sub>reg</sub>	Regulatory T cell
ULN	Upper Limit of Normal
WB	Whole Blood
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

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## Study Summary

Title	A phase II, open-label, single arm, multicenter study of Avelumab with hypofractionated re-irradiation (HFRT) in adult subjects with transformed <i>IDH</i> mutant glioblastoma (GBM)
Short Title	Phase II trial of Avelumab with HFRT in adult transformed <i>IDH</i> mutant GBM
Protocol Number	s16-01179
Phase	Phase 2
Methodology	Multicenter, open-label, single arm, 2 stage phase II study with a safety lead-in.
Study Duration	Approximately 24 months from start of screening to last subject processed and finishing the study)
Study Center(s)	Multicenter. Four sites: 1) Perlmutter Cancer Center (PCC) at New York University Langone Medical Center (NYULMC) 2) Dana-Farber/Harvard Cancer Center (DF/HCC), which includes Massachusetts General Hospital, Dana-Farber Cancer Institute and Beth Israel Deaconness Medical Center 3) University of California, San Francisco (UCSF) 4) University of California, Los Angeles (UCLA)
Objectives	<p><b>Primary Objectives:</b></p> <ul style="list-style-type: none"> <li>To assess the safety and toxicities of, and recommended phase 2 dose (RP2D) of Avelumab when administered with HFRT in adults with <i>IDH</i> mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy. There will be a Safety Lead-In cohort of 6 patients followed by an expansion cohort in which the primary objective will be;</li> <li>To estimate the 6-month progression-free survival (PFS6) of Avelumab + HFRT in adults with <i>IDH</i> mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy;</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>Assess the safety, toxicities and tolerability of Avelumab + HFRT in adults with <i>IDH</i> mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy;</li> <li>Estimate the 12-month OS, median PFS, Response Rate, and median duration of response;</li> <li>Explore the association of PFS6 with: hypermutation phenotype; proportion of predicted mutation-associated neoantigens among all somatic mutations; tumor PD-L1 expression; baseline and change in regulatory T cell (T<sub>reg</sub>) and myeloid-derived suppressor cell (MDSC) levels</li> </ul>
Number of Subjects	A minimum of 12 subjects and a maximum of 61 subjects will be registered
Diagnosis and Main Inclusion Criteria	Adults with a previously diagnosed lower grade (WHO grade II or III) <i>IDH1/2</i> mutant glioma that has transformed to glioblastoma (GBM, WHO grade IV) after treatment with temozolomide, CCNU or PCV chemotherapy. Refer to Section 4 for complete Inclusion and Exclusion Criteria.

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Study Product, Dose, Route, Regimen	<ul style="list-style-type: none"><li>• Avelumab (MSB0010718C) 10 mg/kg intravenously (IV) every 2 weeks</li><li>• Hypofractionated radiation therapy to a total dose of 25 Gy, delivered in 5 Gy per fraction for 5 consecutive daily fractions</li></ul>
Duration of administration	Avelumab therapy will continue for up to 2 years if tolerated and or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.
Reference therapy	The reference therapies are bevacizumab monotherapy and hypofractionated radiation therapy, each of which is a standard single-modality therapy for recurrent GBM.
Statistical Methodology	<b>Primary Efficacy Analysis:</b> Forty three (43) patients will be enrolled and treated in the phase II portion of this trial. With an optimum 2 stage Simon Phase II design, we can test the null hypothesis that $PFS6 \leq 0.40$ versus the alternative that $PFS6 \geq 0.60$ with $\alpha = 0.05$ (actual $\alpha = 0.047$ ) and power of 80% (actual is 82.7%) with a total of 43 patients. If 7 or fewer subjects achieve PFS6 among 18 patients, the study will conclude at the end of stage 1; if 8 or more subjects achieve PFS6, the trial will continue for up to 43 patients. If 23 or more subjects achieve PFS6 in the total of 43 patients, the therapy will be considered interesting for further study.

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# 1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

## 1.1 Background

### 1.1.1 Study Disease

Gliomas harboring mutations in isocitrate dehydrogenase (*IDH*) 1 (*IDH1*) or *IDH2* are associated with relatively longer survival compared to wildtype *IDH* gliomas.<sup>1,2</sup> However, all *IDH* mutant glioma patients eventually develop secondary glioblastoma (GBM) and the vast majority of patients die from their disease. *IDH* mutant gliomas are particularly devastating as they occur most frequently in the second and third decades of life yet median overall survival times range from as low as 2.1 years to 10 years in large scale studies.<sup>3-6</sup> No effective salvage therapy exists for *IDH* mutant gliomas that have progressed after standard radiation and chemotherapy. Median survival from the time of transformation to secondary GBM is dismal and equivalent to survival of *IDH* wildtype GBM at first recurrence (7-9 months).<sup>7,8</sup>

### 1.1.2 Rationale for PD-L1 Inhibitor in *IDH*-mutant transformed GBM

Cancer immunotherapy agents have emerged as highly effective for the treatment of several cancer types, inducing durable and extensive tumor regressions in otherwise fatal metastatic diseases for some patients. One immunotherapy strategy that has proven effective for several cancer types is enhancement of the anti-tumor immune response using agents that target T cell inhibitory checkpoint receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1, CD279).

Under chronic stimulation, T cells lose effector function and proliferative capacity often due to signal down-regulation as a result of increased expression of immune checkpoint receptors such as PD-1. PD-1 is an Ig superfamily member related to CD28 and CTLA-4 expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals through its cytoplasmic tail to inhibit T cell functions.<sup>9-11</sup> The ligands PD-L1 (also known as B7-H1 and CD274) and PD-L2 can be detected on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells and its expression is greatly up-regulated after activation or interferon treatment. PD-L1 is often expressed on tumor cells, and binding of PD-1 transmits inhibitory signals to the T cell and down-modulates the anti-tumor T cell response.<sup>11</sup> Under normal conditions, PD-1 is expressed on the cell surface of activated T-cells and down-modulate unwanted or excessive immune responses, including autoimmune reactions.

The PD-1/PD-L1 receptor-ligand axis is hijacked by tumors to suppress immune control and mediate tumor immune evasion. PD-1 is expressed on activated peripheral CD4+ and CD8+ T-cells, B-cells, T<sub>regs</sub> and Natural Killer cells.<sup>12</sup> Healthy organs express little (if any) PD-L1, whereas a number of cancers including GBM constitutively and abundantly express PD-L1 and PD-L2.<sup>12,13</sup> More than 70% of recurrent GBMs have prominent diffuse/fibrillary expression of PD-L1,<sup>14</sup> a frequency higher than that observed in melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC).<sup>15-17</sup> GBMs also upregulate PD-L1 expression in circulating monocytes and tumor-associated macrophages (TAMs).<sup>18</sup> Thus, immune checkpoint pathways such as the PD-1/PD-L1 axis are highly attractive target for therapeutic intervention. Indeed, inhibition of the immune checkpoints using antibodies against CTLA-4, PD-1 and PD-L1 have resulted in durable regressions of several types, leading to recent US FDA approvals of several systemic agents.<sup>19-22</sup>

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Although remarkably durable responses have been observed in several cancer types, immune checkpoint therapy has been effective in only subsets of patients with these cancer types, while non-responding patients receive no benefit from these agents. Recently, higher nonsynonymous mutation burden has been associated with clinical benefit to immune checkpoint inhibitors, including PD-1 inhibitors.<sup>23-25</sup> Notably, a recent study demonstrated that hypermutation phenotype resulting from mismatch repair (MMR)-deficiency predicted response to anti-PD-1 therapy in colorectal cancers.<sup>23</sup> In this study, only hypermutant cancers had objective responses. In addition, two biallelic MMR deficiency syndrome pediatric patients with recurrent multifocal GBM were recently reported to have durable responses to anti-PD-1 therapy.<sup>26</sup> Both GBM patients had driver mutations in *POLE* and >20,000 somatic mutations per exome in their tumors.

Recently, we and others have characterized the molecular events that drive the malignant transformation to secondary GBM in *IDH* mutant glioma.<sup>27-32</sup> A subset of tumors acquire mutations in the Rb pathway<sup>27</sup> concomitant with DNA demethylation and activation of RB/cell cycle pathway genes.<sup>29,30</sup> Subsets of tumors also acquire receptor tyrosine kinase amplifications,<sup>28,29</sup> Akt/PI3K pathway mutations,<sup>27-29</sup> *MYC* pathway mutations,<sup>28,29</sup> and P16 deletions.<sup>29</sup> More recent data has demonstrated that therapy significantly influences the genetic landscape associated with malignant transformation in *IDH* mutant glioma. Chemotherapy and radiation are both associated with acquisition of significantly more mutations at progression,<sup>29</sup> and notably, a subset of glioma patients develop the particularly malignant hypermutation phenotype after treatment with temozolomide or PCV chemotherapy, the most common present-day chemotherapies used for glioma therapy.<sup>27,33-35</sup> A majority of lower grade (WHO grade II or III) *IDH* mutant glioma patients treated with temozolomide or PCV develop a hypermutation phenotype at recurrence,<sup>27,29,31,32</sup> and nearly all *IDH* mutant gliomas that transform into GBM (WHO grade IV) after temozolomide or PCV therapy are hypermutant.<sup>27,31,32</sup> Ultimately, temozolomide or PCV therapy of lower grade *IDH* mutant gliomas results in selection of clones that have acquired somatic mutations in DNA mismatch repair genes (80-90% of cases acquire *MSH6* mutations), and these MMR mutant, hypermutated clones subsequently dominate later recurrences which are invariably fatal.<sup>27,31,32</sup> These data provide considerable rationale for anti-PD-1/PD-L1 therapy in *IDH* mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy, a population highly enriched for hypermutant tumors.<sup>27,31,32</sup>

### 1.1.3 Rationale for PD-L1 Inhibitor + Hypofractionated Radiotherapy (HFRT) in transformed *IDH* mutant GBM

Although there appears to be considerable rationale for the use of immune checkpoint inhibitors in gliomas, GBM tumors have a dominant immune suppressive microenvironment that may mediate intrinsic resistance.<sup>36,37</sup> These mechanisms include secretion of immunosuppressive factors, expression of cell surface immunosuppressive factors such as PD-L1, and presence of immune cells that mediate immunosuppression such as tumor-associated macrophages of the M2 lineage and myeloid-derived suppressor cells (MDSCs).<sup>36,37</sup> Indeed, highly variable efficacy has been reported with single agent immune checkpoint inhibitors in preclinical GBM models, with some studies reporting no efficacy.<sup>38-44</sup>

One strategy to reverse the suppression of tumor immune responses involves the use of radiation therapy (RT), which has been shown to augment anti-cancer immune responses and enhance the efficacy of immune therapies in systemic cancer preclinical models and patients.<sup>43-49</sup> Preclinical studies examining combined radiotherapy and checkpoint inhibition indicate that each activate mostly non-redundant immune stimulating mechanisms and the major contribution of radiotherapy appears to be increasing T-cell receptor (TCR) diversity.<sup>48</sup> RT induces major histocompatibility complex (MHC) class I presentation, increases antigen presentation, and increases cytotoxic T cell (CTL) recognition of irradiated cells<sup>50,51</sup> and enhances the diversity of the TCR repertoire of the expanded peripheral T cell clones.<sup>48</sup> A recent study also demonstrated that fractionated radiotherapy leads to CD8+ T-cell-dependent adaptive upregulation of tumor cell PD-L1 expression.<sup>49</sup>

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In preclinical GBM models, the combination of immune checkpoint inhibition and a short course of RT has demonstrated impressive efficacy. RT induces a proinflammatory response to enhance the antitumor efficacy of immunotherapy. RT upregulates surface MHC class I expression, thereby enhancing the presentation of normally suppressed tumor-associated antigens, while also increasing ICAM-1 expression and CXCL16 secretion.<sup>43,52,53</sup> RT also increases tumor-infiltrating lymphocytes (TILs), including 4 fold increases in total CD4+ and 4.5 fold increases in total CD8+ cells, and also mildly increases Natural Killer cell infiltration.<sup>52</sup> Additionally, RT alone can decrease intratumoral T<sub>reg</sub> levels, and RT + anti-PD1 therapy synergize to increase cytotoxic T cell (CTL) infiltration and significantly increase the CTL to T<sub>reg</sub> ratio in the tumors.<sup>43</sup> In orthotopic, syngeneic murine glioma models, combined immune checkpoint inhibitor and short course RT therapy cured a significant fraction of mice, generating robust antitumor immune responses, tumor regressions, long-term survival and antitumor immunity.<sup>43,44</sup>

#### 1.1.4 Rationale for Radiation Treatment Scheme and Schedule with Avelumab

The specific radiation fractionation scheme utilized to stimulate an immune response has also been shown to affect tumor responses to immune checkpoint inhibitor in preclinical studies of melanoma. A three or five fraction regimen of radiation (8 Gy x 3 fractions or 6 Gy x 5 fractions in consecutive days) in one study resulted in superior responses at the primary tumor site compared to a single fraction radiation regimen (20 Gy) when combined with an anti-CTLA4 antibody.<sup>46</sup> In addition, in this preclinical study the three and five fraction regimens induced an "abscopal effect", which resulted in regression in non-irradiated metastases that was not observed with the single fraction regimen.

Per numerous studies and extensive clinical experience, HFRT in regimens similar to that used in this protocol (25-35 Gy x 5 fractions) has a well-established and acceptable tolerability and safety profile in recurrent GBM patients.<sup>54-61</sup> In a recent phase I study, HFRT (30 Gy delivered in 5 fractions) combined with pembrolizumab (an anti-PD1 antibody) and bevacizumab had an acceptable toxicity profile in patient with recurrent high-grade glioma.<sup>62</sup> In patients with melanoma brain metastasis, HFRT combined with immune checkpoint therapy has been reported to be well tolerated and demonstrated preliminary evidence of synergistic activity.<sup>63</sup> An additional potential advantage of using HFRT is that a shorter course of radiation could potentially avoid the sustained immunosuppression that has been reported with prolonged weekly fractionation schedules typically given for adjuvant therapy of high-grade gliomas.<sup>64,65</sup>

The optimal schedule for combining radiotherapy and immune checkpoint inhibitors is currently unclear. No significant differences in efficacy have been observed when immune checkpoint inhibitor was given prior to, concurrent with, or 7 days after RT in glioma and melanoma *in vivo* models.<sup>44,48</sup> However, in one preclinical mouse study using colon cancer xenografts, significant improvements in overall survival were only observed when an anti-PD-L1 antibody was given at day 1 or 5 of a five-day fractionated radiotherapy cycle whereas anti-PD-L1 antibody given 7 days after completion of radiotherapy was completely ineffective at increasing overall survival compared with radiotherapy alone.<sup>49</sup>

#### 1.1.5 Rationale for Study Design and Safety Lead-In:

Hypofractionated Radiotherapy (HFRT) in the schedule used for this trial (25 Gy delivered in 5 fractions) has a well-established safety profile in recurrent GBM (see above **Section 1.1.4** and reference [56]), and similar regimens have been safely provided concurrently with anti-PD-1 antibody therapy in recurrent high-grade glioma patients in a phase I study<sup>62</sup> and in patients with melanoma brain metastases.<sup>63</sup> Therefore, Avelumab is expected to be well tolerated when combined with HFRT. Nevertheless, a 6 subject Safety Lead-In will be conducted to further define the safety and determine the recommended phase II dose (RP2D) of Avelumab when combined with HFRT. The dose of Avelumab administered during the Safety Lead-In will not

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exceed the established recommended phase II dose of Avelumab when administered as monotherapy.

The Safety Lead-In also incorporates a de-escalation of Avelumab dosing if unexpected dose-limiting toxicity is observed in the first 6 subjects that follows a 3+3 phase I design for the dose de-escalation. Avelumab will initially be administered at 10 mg/kg intravenously (IV) every 2 weeks, which is the RP2D established for monotherapy administration. The first 6 subjects will be considered the Safety Lead-In and observed for dose-limiting toxicities (DLTs) for an evaluation period of 28 days (see **DLT** definitions in **Section 5.2.1.2**). If 2 unexpected DLTs are observed in the first 6 subjects, the Safety Lead-In will enter a dose de-escalation phase with subjects enrolled at lower dose levels in groups of 3 in a 3+3 design (see Safety Lead-In study design, **Section 5.2.1**).

### 1.1.6 Summary of Background and Rationale

There is a significant rationale for combining anti-PD-L1 therapy with HFRT for therapy in *IDH* mutant GBM patients who have transformed after temozolomide or PCV chemotherapy, a population that is highly enriched for clonal hypermutant tumors. Although gliomas have a highly immunosuppressive tumor microenvironment, the extremely high number of somatic mutations present within these genetically-defined tumors are more likely to stimulate an anti-tumor immune response, possibly due to the concomitantly higher number of potential mutation-associated neoantigens. A brief course of radiation therapy may increase the presentation of these potential neoantigens by increasing MHC class I presentation and increasing TCR diversity and would also synergize with anti-PD-L1 therapy given their non-redundant mechanisms of anti-tumor immune stimulation.

Preclinical modeling indicates that the optimal dose of radiotherapy to enhance immune checkpoint therapy is a brief course of fractionated radiotherapy (e.g. HFRT) rather than a single fraction of radiation or prolonged fractionated radiation prescriptions given over many weeks. With regards to scheduling, the administration of immune checkpoint therapy either prior to initiation of radiotherapy or concurrent with radiotherapy appears superior to immune checkpoint therapy given after the completion of radiotherapy.

## 1.2 Avelumab

### 1.2.1 General Information

The active pharmaceutical ingredient in Avelumab (MSB0010718C) is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1.

Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

The calculated molecular weight of the molecule is 143,832 Dalton. The antibody is produced by mammalian cell culture in a serum-free growth medium. The antibody is purified by affinity, ion-exchange, and mix-mode chromatography. The process also includes specific viral inactivation and removal steps. The antibody is then transferred into formulation buffer and brought to the desired concentration.

Avelumab will be provided to patients enrolled on this study by EMD Serono/Merck KGaA.

Complete background information on Avelumab and the Avelumab development program can be found in the Investigator's Brochure and the **Pharmacy Manual**.

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### 1.2.2 Physical, chemical, and pharmaceutical properties and formulation

Avelumab drug product is a sterile, clear, colorless and non-pyrogenic concentrate for solution presented at concentration of 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP) type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.

Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).

Avelumab requires further dilution prior to intravenous (IV) infusion. Avelumab infusion solution should be prepared by dilution in 0.9% Sodium Chloride (Normal Saline) (or in 0.45% Sodium Chloride, only if the first option is not applicable). The verified Avelumab concentration range in the infusion solution is 0.016 mg/mL to 8 mg/mL.

For Avelumab drug product, only excipients that conform to the current Ph. Eur. and/or the current USP are used.

### 1.2.3 Instructions for Storage

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long-term stability studies with Avelumab.

Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

In the event of a temperature excursion:

- Inform Fisher Clinical Services immediately by sending a Temperature Excursion Form (provided separately) to: [AvelumabTemperatureExcursion@thermofisher.com](mailto:AvelumabTemperatureExcursion@thermofisher.com)

And

- Quarantine vials until further approval for use is received

### 1.2.4 Handling of the Dosage Forms

#### General Instructions:

To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel to guarantee the sterility of the product to be injected. Only clinical site personnel who are appropriately trained on the procedure may perform the preparation and administration procedures specified in the **Pharmacy Manual**. Clinical site personnel involved in these procedures must comply with all applicable regulations and standards.

#### Safety Precautions:

Handling Information: Recommendation in the Safety Data Sheet (SDS) should be followed. The SDS will be provided separately to the study sites.

Safety Equipment Used: Appropriate gowning and footwear as per local site procedures.

#### Handling Conditions:

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Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature (15-25°C, 59-77°F) preferably for 30-50 min.

Rough shaking of the solution must be avoided. Addition of other medication to the infusion containers containing Avelumab must be avoided. No other drug should be added to the solution for infusion containing Avelumab.

### 1.2.5 Nonclinical pharmacology

Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

The nonclinical pharmacology studies have shown that avelumab functionally enhances T cell activation *in vitro* and significantly inhibits the growth of PD-L1 expressing tumors *in vivo*.

Avelumab binds to human PD-L1 with a high affinity of 0.7 nM and not to any other B7 family proteins, and competitively blocks the interaction of PD-L1 with PD-1. The *in vitro* study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin (IL)-2 or interferon-gamma (IFN- $\gamma$ ) production. In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger the antibody-dependent cell-mediated cytotoxicity (ADCC) against target cells expressing PD-L1.

Avelumab has 2 main mechanisms of action for exerting its anti-tumor effects:

1. PD-L1 on tumor cells can interact with PD-1 or B7-1 on activated T cells. These interactions have been shown to significantly inhibit T cell activities. Therefore, blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can release T cells from immunosuppression, and lead to elimination of tumor cells by T cells.
2. Tumor cells may express high levels of PD-L1 on their surface compared with normal tissues. As a fully human IgG1 monoclonal antibody (mAb), Avelumab has ADCC potential. Upon binding to PD-L1 on tumor cells and binding with their Fc part to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC.

Therefore, blocking PD-L1 inhibitory mechanisms by interactions with not only PD-1 but also the other ligand, B7-1, avelumab offers unique therapeutic potential compared with mAbs targeting PD-1.

### 1.2.6 Nonclinical pharmacokinetics and metabolism

Avelumab exhibits the expected pharmacokinetic (PK) profile for an antibody binding to a cellular target with combined first order catabolic clearance and saturable target-mediated clearance in mice and monkeys. Due to the lower  $K_M$  value for monkey the non-linear pathway is already saturated at lower Avelumab concentrations than in mice. Volume of distribution of Avelumab was low and in the range of the serum volume. Similar  $t_{1/2}$  of around 60 to 70 hours at doses between 20 and 140 mg/kg were observed in toxicity studies in mice and monkeys.

As avelumab represents a foreign protein to the immune system of animals, anti-avelumab antibodies in rodents and non-human primates were observed and have been considered in interpreting the nonclinical data. 40.5% to 100% of mice, 22.2% of rats, and up to 100% of monkeys treated with the drug developed anti-drug antibodies (ADAs). In animals, the generated ADAs seem to have the potential to increase the clearance of the avelumab. It should be emphasized that immunogenicity of the human avelumab in animals is not deemed predictive for the human situation.

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### 1.2.7 Nonclinical toxicology

The toxicological profile of Avelumab was investigated *in vivo* in mice, rats, and cynomolgus monkeys (Studies RF2710, RF2740, RF4990, RF3310, and T16228). In addition, an *in vitro* cytokine release assays (CRA) in human and cynomolgus monkey whole blood and PBMCs (Studies T17985, T17986, and 14-DA471-N0) as well as a tissue cross reactivity study in normal human and cynomolgus monkey tissues was performed (Study 20015186 and Study 20015187). These studies are described in detail in the Investigator's Brochure.

On the basis on the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of avelumab. However, in the repeat dose-toxicity studies in CD-1 mice with Avelumab IV bolus injection mortality occurred mainly after the third administration. A mechanistic study supported the hypothesis that the mortalities are caused by an immune-mediated hypersensitivity reaction, the mechanism of which is highly likely to be anaphylaxis (immunoglobulin E [IgE]/IgG mediated reaction). Due to severe hypersensitivity reactions after repeated administration in mice and the low binding affinity in rats, rodent species are not considered appropriate for nonclinical safety testing of avelumab and therefore, a single species approach (cynomolgus monkey only) is envisaged.

Accordingly, repeat dose-toxicity studies of 4 and 13 weeks duration have been conducted in cynomolgus monkeys. Neither in the pilot 4-week IV repeat-dose toxicity study nor in the pivotal 13-week study, clinical signs of hypersensitivity have been seen after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg, respectively. For the pilot 4-week study as well as for the pivotal 13-week IV repeat-dose toxicity study, a NOAEL of 140 mg/kg for systemic toxicity was established. Available toxicokinetic data in monkeys showed a  $t_{1/2}$  of 60 to 70 hours and linear kinetics of avelumab in this species.

Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed no clear-cut evidence for release of pro-inflammatory cytokines. However, a subsequent, optimized CRA demonstrated evidence of potential cytokine release in PHA pre-stimulated PBMCs. Clinical experience has demonstrated that the relative risk of an infusion reaction is low (approximately 2%) and with premedication drops to a very low level (less than 1%) indicating that the optimized CRA substantially overestimates the risk of cytokine release in a clinical setting.

### 1.2.8 Clinical safety

Avelumab is currently in clinical development across Phases I, II, and III. The Avelumab Investigator's Brochure reports safety data from the following 4 clinical trials:

- EMR 100070-001: A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
- EMR 100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer
- EMR 100070-003: A Phase II, single arm, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma (MCC)
- EMR 100070-004: A Phase III open-label, multicenter trial of avelumab versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet

More than 1500 subjects have been enrolled in the EMR 100070-001 trial. The 3 + 3 dose escalation algorithm to determine the MTD is complete and a dose of 10 mg/kg once every 2

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weeks was determined for the tumor expansion cohorts on the basis of safety, PK, and PD observations. The treatment expansion part of the trial consists of 16 tumor treatment cohorts. As of 05 November 2015 (data cutoff for a pre-planned safety data review by the study Safety Monitoring Committee [SMC]), 53 subjects in the dose escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0 mg/kg of avelumab, respectively) and 1300 subjects in the pooled expansion part had received 10 mg/kg avelumab and were followed up for at least 4 weeks.

The safety summary from the Investigator's Brochure summarizes data from 1300 subjects treated in the pooled treatment expansion cohort from the ongoing Phase I Trial EMR 100070-001 (as of 05 November 2015). The pooled data included subjects treated in all tumor expansion cohorts, including non-small cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck. Safety data are also summarized for 52 subjects in the ongoing Phase I Trial EMR 100070-002 and for 88 subjects in the ongoing Phase II Trial EMR 100070-003 (as of 17 December 2015). For Trial EMR 100070-004, an overview of the serious adverse events (SAEs) is provided.

Most of the observed adverse events (AEs) were either in line with those expected in subjects with progressive advanced solid tumors or with class effects of mAb blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab.

For a summary of the clinical safety data observed with the planned Avelumab dosing for this trial, see the **Clinical Safety Data Related to Dose** summary in **Section 1.4**.

### 1.2.9 Clinical Efficacy

The clinical efficacy information summarized in the Avelumab Investigator's Brochure includes data from the NSCLC and ovarian cancer expansion cohorts of the ongoing Phase I Trial EMR 100070-001, and for 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Trial EMR 100070-002.

The NSCLC expansion cohort in the ongoing Phase I Trial EMR 100070-001 had a cutoff date of 15 January 2015, 6 months after start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). The objective response rate (ORR) based on confirmed and unconfirmed responses for subjects treated in the NSCLC expansion cohort was 14.1% (26 of 184 NSCLC subjects). Progression free survival (PFS) and overall survival (OS) were all evaluated for all NSCLC subjects treated in the expansion phase. As of 15 January 2015, the median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively.

The clinical activity of avelumab was also evaluated by subjects' tumor PD-L1 expression status in the NSCLC expansion cohort. An objective response was observed in 20 of 122 subjects (16.4%) who were PD-L1 positive (defined as having at least 1% PD-L1 positive tumor cells) compared with 2 of 20 subjects (10.0%) who were considered PD-L1 negative (defined as having less than 1% PD-L1 positive tumor cells). A longer median PFS (12.0 vs. 5.9 weeks) and OS (8.9 vs 4.6 months) were both observed in PD-L1 positive compared with PD-L1 negative subjects.

The ovarian cancer expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last subject who was included in this pre-planned interim analysis on this expansion cohort. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 subjects). The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95% confidence interval (CI): 6.3 to 12.0 weeks).

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The preliminary efficacy data for the ongoing Phase I Trial EMR 100070-002 are based on a data cutoff of 11 March 2015. As of the data cutoff, 3 of 20 subjects responded to trial treatment (all responses were partial responses [PRs] and all responses were confirmed responses), and the best overall response (BOR) was 15.0% (95% CI: 3.2% to 37.9%). The median PFS of this group was 11.9 weeks (95% CI: 6.0 to 12.3 weeks).

### **1.3 Preclinical Data**

#### **1.3.1 Preclinical Efficacy of Avelumab**

The antitumor activity of avelumab has been investigated in various murine tumor models. Inhibition of the PD-1/PD-L1 interaction is proposed to exert a therapeutic effect by restoring anti-tumor CD8+ T cell responses (refer to Avelumab Investigator's Brochure). To circumvent the need for a surrogate antibody, the lead candidate antibody was specifically selected for cross-reactivity to murine PD-L1, and, as consequence all of the nonclinical studies were conducted in syngeneic murine tumor models in which the immune system of the host is fully intact. It was demonstrated that the inhibition of the PD-1/PD-L1 interaction restores anti-tumor CD8+ T cell responses, which results in an anti-tumor activity.

Avelumab has demonstrated significant nonclinical activity as a monotherapy and in various combination therapy settings. In general, the anti-tumor immunotherapy via blockade of the PD-1/PD-L1 axis seems not to be limited to any specific tumor types. As a monotherapy, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. A dose-dependent trend was observed, and 400 µg per dose (20 mg/kg, approximately) was identified as the optimally effective dose when given every third day for 3 total doses.

The *in vivo* anti-tumor effects were found to be primarily mediated by CD8+ T cells as evidenced by the observation that *in vivo* depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of ADCC as a potential mechanism of anti-tumor activity was further demonstrated *in vivo* using a deglycosylated version of avelumab to abrogate fragment crystalline (Fc) receptor binding or via the systemic depletion of natural killer (NK) cells. In both settings, loss of *in vivo* ADCC potential significantly reduced the anti-tumor activity.

The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy, resulted in an improved anti-tumor activity. Chemotherapy with combination therapy (with folinic acid, 5-fluorouracil, and oxaliplatin [FOLFOX], and radiation therapy showed the better tumor growth inhibition. In particular, radiation therapy was found to be a highly synergistic combination with avelumab capable of causing complete regression of established tumors probably through generating anti-tumor immune memory.

Various immunomonitoring assays were incorporated into the *in vivo* studies. Treatment with avelumab resulted in a consistent increase in the percentage of CD8+PD-1+ T cells and an increased frequency of CD8+ T cells with an effector memory (TEM) phenotype as determined by flow cytometry. Furthermore, these changes correlated with the anti-tumor effect. Increases in tumor antigen-specific T cell responses, as measured by enzyme-linked immunosorbent spot and pentamer immunoassays, were evident following treatment with avelumab and these responses were enhanced when combined with FOLFOX or radiation. Hence, increases in CD8+PD-1+ T cells, CD8+ TEM cells, and antigen-specific T cell responses, may be leveraged as pharmacodynamics (PD) biomarkers with translational relevance to the clinical setting.

#### **1.3.2 Preclinical efficacy of PD-1 inhibition and radiation therapy in gliomas**

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The combination of immune checkpoint inhibitor therapy and a short course of radiation therapy has shown impressive efficacy against orthotopic, immunocompetent murine GBM models (see also **Section 1.1.4**). In one study using focal single fraction radiation therapy followed by an anti-PD-1 antibody, significantly improved survival time was observed in mice receiving radiation plus anti-PD-1 antibody compared to either treatment alone or no treatment (control).<sup>43</sup> Median survival was 25-28 days in the control, anti-PD-1 antibody, and radiation arms, and 53 days in the radiation plus anti-PD-1 antibody arm ( $P < .05$ ). Additionally, long-term survival (>180 days) was observed in 15%-40% of mice in the combination therapy arm. Immunologic data on day 21 after implantation showed increased tumor infiltration by cytotoxic T cells and decreased T<sub>regs</sub> in the combination therapy group compared with the single modality arms. Furthermore, mice that had received combination therapy demonstrated evidence of long-term anti-tumor immunity. Combination therapy-treated mice that survived >90 days after implantation were re-challenged with the same GBM cell line in the flank and compared with treatment naive mice. While flank tumors in naive mice developed large tumors by day 20, none of the mice that had previously received combination therapy grew tumors by day 60.

Another study in orthotopic, immunocompetent murine GL-261 GBM models demonstrated that the combination of radiation therapy and immune checkpoint inhibition was required to see survival benefit over either modality alone.<sup>44</sup> In this study, immune checkpoint modulation using an anti-CTLA-4 antibody and/or a 4-1BB activating antibody was compared to focal single fraction radiation therapy alone and various combinations of all 3 agents. In various experiments, only groups that received radiation with immune checkpoint modulation (anti-CTLA-4 with/without 4-1BB activating antibody) had subsets of mice with long-term survival. Median overall survival was significantly increased in groups that received combination therapy with radiation and anti-CTLA-4 antibody compared to groups receiving no treatment, radiation alone, or immune checkpoint modulation alone (anti-CTLA-4, anti-4-1BB, or both antibodies). In addition, mice that received combination immune checkpoint inhibition and radiation therapy and survived >100 days after implantation demonstrated anti-tumor immunity, as none of these mice developed tumors when re-challenged with the same GBM cell line subcutaneously into the flank, while all treatment-naive mice developed large tumors. In this study, the systemic anti-tumor memory was also shown to be glioma-tumor specific, as a melanoma cell line injected subcutaneously into the opposite flank of both long-term surviving mice and naive mice developed into tumors in all the mice regardless of prior treatment.

## 1.4 Dose Rationale

A dose of 10 mg/kg of Avelumab, intravenous (IV) once every 2 weeks, was selected for the expansion cohorts of Phase I trials, the Phase II pivotal trial (EMR 100070-003), and the ongoing Phase III trials based on the preliminary pharmacokinetic (PK), target occupancy, and preliminary clinical safety data collected in the clinical trials. For complete details, refer to the Avelumab Investigator's Brochure (also **Section 1.2.5**).

Avelumab plasma levels leading to full programmed death ligand 1 (PD-L1) receptor target occupancy (TO) on PBMCs resulted in tumor growth inhibition in a murine disease model. Therefore, full TO on PBMCs can be considered a PD marker for the ability of Avelumab to act on its target and to show clinical activity.

Preliminary PK data from EMR 100070-001 show that the concentration at the end of dose interval ( $C_{min}$ ) increased more than proportionally to dose between 1 to 10 mg/kg, but proportionally for doses above 10 mg/kg. Consistently the  $t_{1/2}$  also increased with the dose. However, the average value was 102 and 120 hours for 10 mg/kg and 20 mg/kg, respectively, with no significant difference between these two dose groups. This PK characteristic suggests that target mediated drug disposition is involved in the clearance of Avelumab and a high PD-L1 TO is likely achieved at the trough concentration for doses of 10 mg/kg and 20 mg/kg.

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The *in vitro* target occupancy data further support that a high TO is likely achieved at 10 mg/kg and above.

- Target occupancy was measured *ex vivo* by flow cytometry on peripheral blood CD3<sup>+</sup> T cells from patients (n=9) treated with Avelumab. After the first dose of the initial dose-escalation portion of Trial EMR 100070-001, the observed mean TO reached a plateau of about 90% on Day 15 pre-dose for dose levels of 3 mg/kg and above.
- In addition, *in vitro* TO was measured using flow cytometry on peripheral blood CD3<sup>+</sup> T cells from 8 healthy volunteers after spiking Avelumab over a concentration range of 0.003 to 10 µg/mL. A 50% TO was observed at a drug concentration (standard deviation [StD]) of 0.122 (0.042) µg/mL, and a concentration of 1 µg/mL Avelumab was required for > 95% target occupancy. Based on these data and the trough serum levels observed in EMR 100070-001, TO was projected to reach or exceed > 95% throughout the entire dosing interval for 10/13 subjects at 3 mg/kg, and for all (15/15) subjects at 10 mg/kg group from dose escalation group in EMR 1000700-001.

Based on the *ex vivo* peripheral blood CD3<sup>+</sup> T cell and *in vitro* target occupancy results, the dose of 10 mg/kg every 2 weeks is expected to achieve target saturation during the entire dosing interval in the majority of patients.

### **Clinical Safety Data Related to Dose**

As of the safety cutoff date of 05 November 2015, 1353 subjects have received at least 1 dose of Avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, of which 1315 have received the proposed dose of 10 mg/kg (15 in the dose escalation part of the study and 1300 subjects in the pooled expansion cohort).

In the dose escalation portion of the Phase I study, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached. Ongoing review of the safety data by the Safety Monitoring Committee (SMC) suggests an acceptable safety profile of Avelumab administered at the 10 mg/kg every 2 weeks dose and schedule.

Treatment-related treatment-emergent adverse events (TEAEs) were observed in 813 (62.5%) subjects in the pooled expansion cohort. The most frequently observed treatment related TEAEs (incidence >5%) were:

- Fatigue (212 subjects, 16.3%)
- Infusion-related reaction (209 subjects, 16.1%)
- Nausea (108 subjects, 8.3%)
- Chills (102 subjects, 7.8%)  
Diarrhea (79 subjects, 6.1%)
- Pyrexia (72 subjects, 5.5%).

Grade ≥3 treatment-related TEAEs were observed in 124 subjects (9.5%) in the pooled expansion cohort. The most frequently reported Grade ≥3 treatment-related TEAEs were:

- Gamma-glutamyl transferase increased (GGT) (9 subjects; 0.7%)
- Infusion-related reaction (9 subjects; 0.7%).

Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of Avelumab. The safety profile of Avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

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In conclusion, preliminary data from EMR 100070-001 showed that Avelumab at doses up to 20mg/kg IV every 2 weeks was well tolerated, and the dose of 10 mg/kg IV every 2 weeks was considered to have an acceptable safety profile for further investigation in clinical studies.

### **Conclusion:**

Based on the PK results and the receptor occupancy data, sufficient trough concentrations appear to be achieved for full TO in the blood in the majority of subjects receiving the 10 mg/kg dose. Within the dose range of 1 mg/kg to 20 mg/kg, Avelumab was well tolerated and is deemed to have an acceptable safety profile.

Based on the above analyses, a dose of 10 mg/kg IV once every 2 weeks was considered to have a favorable risk benefit profile and thus represents an appropriate dose for further investigation in registration studies of Avelumab.

## **1.5 Research Risks & Benefits**

### **1.5.1 Risk of Avelumab administration**

Most of the observed adverse events (AEs) for Avelumab were either in line with those expected in subjects with progressive advanced solid tumors or with class effects of mAb blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for Avelumab. For details regarding the risks and clinical safety profile of Avelumab, see **Section 1.2.8** and the **Dose Rationale, Section 1.4**.

To minimize risk to the subject, vital signs, symptom-directed physical exams and safety labs will be performed at frequent intervals throughout the study and as indicated in the **Schedule of Events (Attachment 1)**. Pre-medication will be given prior to every Avelumab infusion, and risk mitigation measures for infusion-related reactions will be implemented in this study consistent with all ongoing clinical studies with Avelumab. In addition, subjects will be asked to report any potential adverse events and concomitant medications continually throughout the study as indicated in the Schedule of Events, and complete physical exams performed prior to the initiation of every cycle. Furthermore, investigators will be educated on expected **immune-related adverse events (irAE)** as defined in **Section 5.2.3.3** as well as **adverse events of special interest (AESIs)** as defined in **Section 3.4**. A table is included that describes specific irAEs and provides supportive care, dose modification and discontinuation guidelines for Avelumab-related adverse events (**Attachment 4**).

### **1.5.2 Risk with Radiation Therapy (RT)**

Salvage re-irradiation has long been offered as a treatment modality for recurrent GBM patients and has been established to be generally safe and well tolerated (see Section 1.1.4). However, the risk of radiation necrosis and other adverse events listed below are increased in the setting of re-irradiation for glioma.

Expected acute radiation therapy adverse events include skin reaction, including dryness, redness, itching (pruritis), tanning, soreness and hair loss, fatigue, nausea, vomiting, dry mouth, altered taste, decrease in blood counts, short-term hearing impairment due to reactions in the ear canals and on the ear, serous otitis media (fluid in the middle ear) as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness.

Expected early delayed radiation therapy adverse events (occurring 1-3 months after radiotherapy treatment) include fatigue, lethargy and transient worsening of existing neurological deficits.

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Expected late delayed radiation therapy adverse events (occurring 3 months or more after radiation therapy treatment) include radiation necrosis (severe local damage to normal brain tissue), which may result in permanent neurocognitive deficits (difficulties with short term memory, calculations, language and more severe neurocognitive deficits) or motor dysfunction, leukoencephalopathy, permanent hearing impairment, radiation injury to the visual structures including the optic nerve and chiasm, which can result in partial or complete blindness, cataracts endocrine dysfunction and radiation-induced neoplasms. Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.

To minimize risk to the subject, modern RT techniques will be used including fractionated stereotactic radiotherapy, protons, and IMRT, which allow for highly conformal treatment to a considerably more precise target volume. These technologies have the potential to significantly reduce the toxicity associated with re-irradiation.<sup>66</sup> Fractionated and hypofractionated RT (HFRT) have well-established safety and adverse event profiles and is generally well tolerated in recurrent GBM patients, with uncommon occurrences of late CNS toxicity and radiation necrosis (see **Section 1.1.4**).

### 1.5.3 Potential Overlapping Toxicities with Avelumab and Re-Irradiation

There is a theoretical risk that immunotherapy may potentiate the effects of central nervous system radiation necrosis given that radiation-related central nervous system necrosis is partially immune-mediated.<sup>67-69</sup> Thus, there is potential for increased frequency of cerebral radiation necrosis and severe neurotoxicity from cerebral radiation necrosis. This potential for overlapping toxicity may also result in an increased risk of surgery for diagnosis and treatment of radiation necrosis.

However, a recent phase I study has demonstrated that HFRT can be safely combined with anti-PD-1 antibody therapy in recurrent high-grade glioma patients<sup>62</sup> and a retrospective study has reported that anti-PD-1 antibody therapy can be safely combined with various hypofractionated radiation prescriptions in melanoma brain metastasis patients.<sup>63</sup>

Therefore, we will conduct a **Safety Lead-in** (see **Section 1.1.5** for rationale) that will include the first 6 subjects to further define the safety and determine the RP2D of Avelumab when combined with HFRT. The dose of Avelumab administered during the safety lead-in will initiate with the established RP2D of Avelumab when administered as monotherapy and incorporates a de-escalation of Avelumab dosing following 3+3 phase I guidelines if unexpected DLT is observed in the first 6 subjects.

### 1.5.4 Other Risks of Study Participation

Beyond the risk of study therapy exposure, subjects will not be exposed to additional risk beyond the risks associated with standard of care safety procedures for recurrent GBM therapy. The study procedures including subject visits, vital signs, phlebotomy approximately every 2 weeks, and imaging/response assessments approximately every 2 months, are equivalent to the procedures that would be performed for standard therapy for recurrent GBM. An alternative course of management would be no interventional therapy and palliative care only. Compared to palliative care, the risks associated with study participation outside of study therapy exposure include the risk of phlebotomy, imaging response assessments including cranial MRI and CT, and visits with practitioners. Risks associated with phlebotomy include weakness, redness, pain, bruising, bleeding, or infection at the needle site. To minimize risk, patients will be counseled on study procedures and associated risks throughout the duration of the study.

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Risk of harm from genetic testing may be a possibility should the principal investigator identify important findings in the future research and the subject opt into receiving these results. Genetic testing can generate information about a subjects' personal health risks and can cause or increase anxiety, damage family relationships, and/or compromise insurability, employability and can even lead to discrimination. Results will only be disclosed by a qualified genetic counselor under the circumstance that the PI believes they are important for the subject's health, and results will not be shared with employers, insurers, or placed in the subject's medical record, thereby greatly reducing the possibility of psychological or social risks that could arise from knowledge of this genetic information, such as risk for employability or insurability or the risk of discrimination.

### 1.5.5 Potential benefits

The potential benefits to subjects with study participation are improved tumor control and improved overall survival with study participation. Currently there is no effective therapy for secondary, recurrent *IDH* mutant glioblastoma that has transformed after chemotherapy including temozolomide and PCV. No therapy has been proven to improve survival in this setting in a randomized, prospective trial.

## 2 Study Objectives

This is a single arm, open-label phase II study with a 6 patient safety lead-in cohort with the primary objective of determining the safety and toxicities of, and recommended phase 2 dose (RP2D) of Avelumab when administered with HFRT in adults with *IDH* mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy. An additional primary objective will be to estimate the PFS6 of the study therapy (Avelumab + HFSRT) in a two stage phase II trial design. Secondary objectives will be to estimate additional measures of efficacy, including 12-month OS, median PFS, radiographic response rate, and median duration of response, as well as explore the association of biomarkers with PFS6, including hypermutation phenotype, proportion of predicted mutation-associated neoantigens, tumor PD-L1 expression, and circulating baseline and changes in T<sub>reg</sub> and MDSC levels.

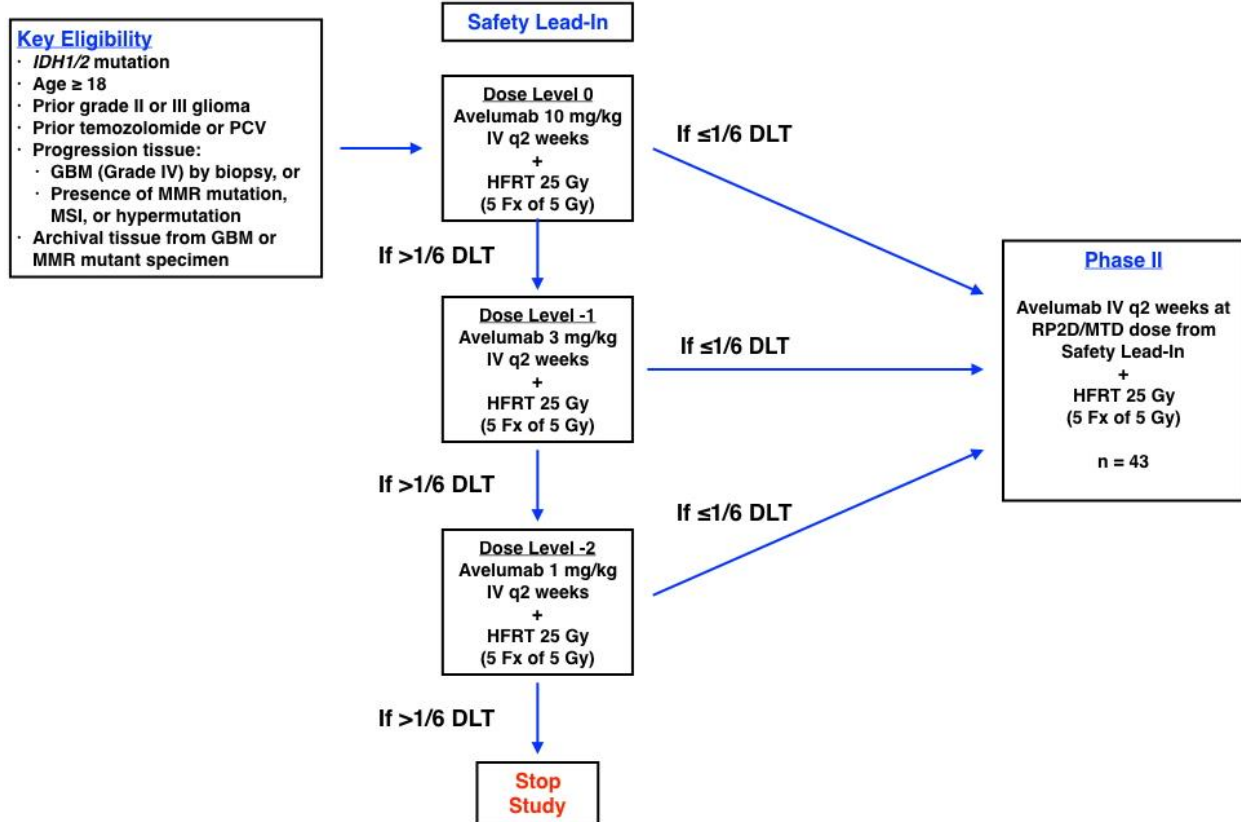
## 3 Study Design

### 3.1 General Design

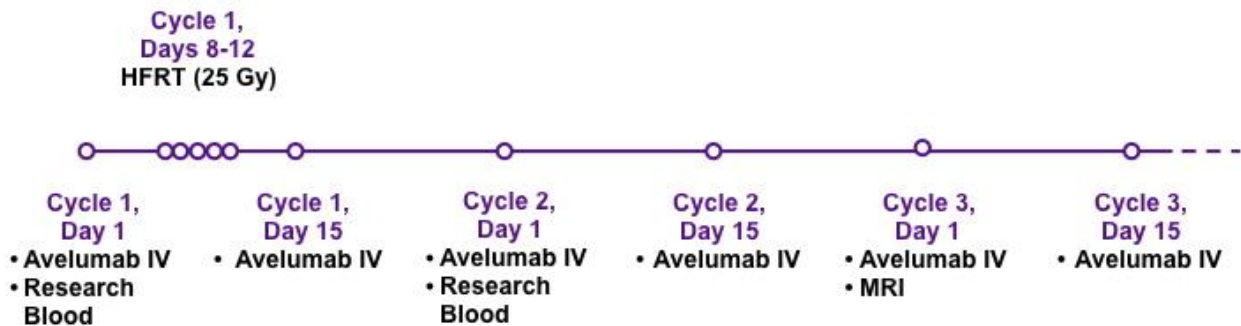
#### 3.1.1 Study Schema

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### Timeline of Selected Important Events



### 3.1.2 General Study Design

This is a multicenter, single arm, open label, phase II trial of Avelumab and radiation in adult patients with transformed *IDH* mutant GBM with the primary objective of estimating PFS6.

The study will start with a **Safety Lead-In (Section 5.2.1)**, which will be conducted to further define the safety and determine the recommended phase II dose (RP2D) of Avelumab in a subsequent expansion cohort when combined with HFRT. The Safety Lead-In also incorporates a de-escalation of Avelumab dosing if unexpected dose-limiting toxicity is observed in the first 6 subjects and follows a 3+3 phase I design. The first 6 subjects will be considered as a Safety Lead-In and will be observed for dose-limiting toxicities (DLTs) for an evaluation period of 28

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days. The dose of Avelumab administered during the Safety Lead-In will not exceed the established RP2D of Avelumab when administered as monotherapy.

The **Phase II trial (Section 5.2.2)** is a two-stage design study at the Avelumab dose determined to be safe in combination with HFRT (RP2D) in the Safety Lead-in. The phase II trial will enroll a total of 18 subjects in stage 1. In interim evaluation for efficacy will be conducted at the end of stage 1. If the efficacy measures are met, 25 additional subjects will be enrolled in stage 2 for a total planned enrollment in the phase II trial of 43 patients. Monitoring of toxicity will be carefully assessed during the phase II trial (see Primary Safety Endpoints, **Section 3.4**). For study purposes, the occurrence of toxicity attributable to Avelumab that requires discontinuation of Avelumab therapy as defined in **Section 5.2.3.2** is defined as unacceptable. Dose limiting toxicity rates of 40% or less are considered acceptable. Interim analyses of safety will be conducted at 10 patients and again at 18 patients as described in the Primary Safety Endpoints (**Section 3.4**).

After screening procedures and registration, subjects will be treated with one dose of Avelumab (10 mg/kg IV) followed by hypofractionated radiotherapy (HFRT, 5 fractions of 5 Gy each fraction on consecutive days) that initiates 7 days after the first dose of Avelumab. Avelumab will continue to be given once every 2 weeks after the first dose. One treatment cycle is defined as 28 days, corresponding to 2 doses of Avelumab. Subjects will be evaluated every 8 weeks with radiographic imaging to assess response to treatment. The Immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria (**Attachment 3**), which is based on the immune-related response criteria and the RANO criteria for brain tumor response assessment, will be used as the primary efficacy endpoint of PFS<sup>6,70</sup>. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Avelumab administration will continue for 2 years or until progression of disease, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements. Expected duration of subject participation is 4 months, which is the median progression-free survival for standard therapy in recurrent GBM.

End of treatment assessments will be performed within 7 days after last drug administration or within 7 days after decision to end treatment. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring and 90 days for serious adverse event reporting. All subjects will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last study drug. Assessments may continue for ongoing reportable adverse events. All subjects will be followed by telephone contact every 3 months or medical record review for overall survival until death.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the **Schedule of Events (Attachment 1)**.

### **3.2 Primary Study Endpoints**

- 1. Determine the safety and tolerability and RP2D of Avelumab when administered with HFRT in adults with *IDH* mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy.**

A Safety Lead-In will be conducted that incorporates a de-escalation of Avelumab dosing if unexpected dose-limiting toxicity (**DLT, Section 5.2.1.2**) is observed in the first 6 subjects and follows a 3+3 phase I design for dose de-escalation, if necessary (see **Section 5.2** for details). The first 6 patients will be considered as safety lead-in and observed for an evaluation period of 28 days. Patients who experience DLT will be discontinued from study therapy and will enter the post-study follow-up phase of the study. To be evaluable for a DLT, an individual subject must

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have received at least the first administration of Avelumab, complete HFRT per protocol and be monitored for at least 28 days following the first Avelumab administration.

The safety analysis will include all subjects who experience toxicities as defined by CTCAE 4.03 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received Avelumab with HFRT, including serious adverse events (**SAEs, Section 8.1**), immune-related adverse events (**irAEs, Section 5.2.3.3**), and adverse events of special interest (**AESIs, Section 3.4**). The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays, will be analyzed to determine if a given toxicity should be considered a DLT for dose de-escalation purposes. Adverse events that meet DLT criteria but occur outside the DLT window will be classified as unacceptable AEs and study treatment will be discontinued.

**2. Estimate the PFS6 of Avelumab + HFRT in adults with *IDH* mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy**

Once the RP2D has been determined, the phase II portion of the study will be conducted. The phase II trial is a two-stage design, single arm trial to estimate the 6-month progression-free survival PFS6 with Avelumab in combination with HFRT in adults with *IDH* mutant glioma that has transformed to GBM (Grade IV) after prior treatment with temozolomide or PCV (see **Statistical Methods, Section 7.2** for details). PFS6 is a standard outcome measure for recurrent glioblastoma clinical trials.<sup>71</sup> The iRANO criteria (**Attachment 3**), which is based on the immune-related response criteria and the RANO criteria for brain tumor response assessment, will be used to assess the primary efficacy endpoint of PFS6. All subjects that receive at least 1 dose of Avelumab and/or radiation will be included in the primary analysis.

### **3.3 Secondary Study Endpoints**

- **Assess the safety and tolerability of Avelumab + HFRT in adults with *IDH* mutant gliomas that have transformed to GBM after temozolomide or PCV chemotherapy.**

An important secondary objective of this study is to characterize the safety, toxicities and tolerability of Avelumab when administered with HFRT among subjects with transformed *IDH* mutant GBM beyond the Safety Lead-In. A safety analysis of the phase II portion of the trial will include all subjects who experience toxicities as defined by CTCAE 4.03 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received Avelumab with HFRT, including serious adverse events (SAEs), immune-related adverse events (irAEs) and AESIs.

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.03. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, and fatal AEs. Furthermore, irAEs and AESIs will be collected and designated as adverse events as described in **Section 3.4** and **Section 5.2.3.3**. For statistical details of the **Primary Safety Endpoint** for the phase II trial, see **Section 3.4**.

- **Estimate the 12-month OS, median PFS, Response Rate, and median duration of response.**

To further define efficacy of Avelumab + HFRT in this study population, secondary measures of efficacy will be assessed, including 12-month overall survival (OS), median progression-free survival (PFS), the radiographic response rate and median duration of response. The subjects treated at the RP2D in the Safety Lead-In will be included as a separate cohort for the evaluation of outcomes in the phase II study. See **Statistical Methods, Section 7.2**, for details of these secondary study endpoints.

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- **Association of PFS6 with: hypermutation phenotype; proportion of predicted mutation-associated neoantigens among all somatic mutations; tumor PD-L1 expression; baseline and change in regulatory T cell (T<sub>reg</sub>) and myeloid-derived suppressor cell (MDSC) levels.**

For complete details of laboratory correlative secondary endpoints, including background and rationale, handling/shipping of research specimens and description of the methods, see **Attachment 7** and the **Lab Manual**.

### 3.4 Primary Safety Endpoints

For the overall endpoints of the Safety Lead-In portion of the study, see **Section 3.2.1**. Safety summaries will be reported for both the Safety Lead-in and the phase II trial. All subjects who received at least one dose of Avelumab and/or radiation will be used for the analysis of safety data in this study. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs.

For the phase II portion of the study, we consider a rate of toxicity of 40% or greater (defined as CTCAE grade 3, grade 4, or intolerable grade 2 toxicity that is possibly, probably, or definitely related to study therapy) to be unacceptable. We will conduct an interim assessment for safety after 10 patients are treated for at least 2 cycles (56 days) and again after 18 patients are treated for at least 2 cycles (56 days). If there are 7 or fewer unacceptable toxicities among the first 10 patients, the trial will continue and not be stopped for safety. After safety analysis of 18 patients, the trial will continue if there are 11 or fewer patients with an unacceptable toxicity. These analyses are not adjusted for multiple assessments and at each analysis, there is a 5% alpha level and 80% power. At the conclusion of the trial, with 43 patients, the trial would be considered to have an unacceptably high toxicity rate if 24 or more patients experienced the specified toxicities.

Due to a possible increased incidence of CNS toxicity from delayed radiation necrosis or radiation injury occurring during the first 6 months post RT, a special interim analysis will be performed. After the first 20 subjects treated at the RP2D, including subjects in the Safety Lead-In portion of the trial, have a minimum 24 week overall survival follow-up time from the end of RT, an interim safety analysis for delayed treatment-induced neurotoxicity will be performed. If the incidence of CTCAE grade  $\geq 3$  CNS (neurologic) toxicity deemed possibly, probably, or definitely related to treatment is 30% or higher in this group, the trial will be halted due to lack of safety.

Additionally, for safety summary purposes, specific **immune related adverse experiences (irAEs)**, as defined **Section 5.2.3.3**) and **adverse events of special interest (AESI)**, as defined below) will be collected and summarized in separate tables from other AEs by toxicity grade and will include the counts, percentage, and 95% CI. Any AE of unknown etiology associated with Avelumab exposure will be evaluated to determine if it is of a potentially immunologic etiology.

**Adverse events of special interest (AESI)** in this study will be defined as:

- Any AE that meets Dose-Limiting Toxicity (DLT) criteria (see **Section 5.2.1.2**)
- Grade 2 or greater infusion-related reactions (See **Section 5.2.3.5**)
- Grade 2 or greater allergic/hypersensitivity reactions (see **Section 5.2.3.5**)
- Grade 3 or greater symptoms suspected to be attributable to brain edema (see **Section 5.2.1.2** for **Rules for Brain Edema**).
- Grade 3 or greater immune-related toxicities (irAEs) (see **Section 5.2.3.3**)

All AESIs must be reported to the study **sponsor** within 24 hours of awareness of the event per **Section 8.3.1**. AESIs should be reported to the local institution's DSMC and IRB per local institution guidelines. If the AESI is **not** a DLT or SAE, there is no need to report to the DSMC or IRB within 24 hours unless specified by the local institution's DSMC or IRB.

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Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory, and vital sign parameters will be summarized with descriptive statistics (counts, percentage, mean, standard deviation, etc.). Continuous measures such as changes from baseline in laboratory, and vital signs parameters will be summarized using descriptive statistics (mean, standard deviation, etc.) for baseline, on-treatment, and change from baseline values.

## 4 Subject Selection and Withdrawal

### 4.1 Inclusion Criteria

1. Male or female subjects aged  $\geq 18$  years.
2. Documentation of *IDH1* or *IDH2* mutation in any tumor specimen.
3. Pathologic evidence (either diagnostic pathology slides or pathology report) of a diagnosis of WHO grade II or III glioma prior to treatment with temozolomide or PCV chemotherapy.
4. Histopathological evidence of glioblastoma (WHO grade IV) on a progressive tumor specimen after treatment with temozolomide or PCV chemotherapy. The diagnosis of glioblastoma must be confirmed on central review by a study-designated neuropathologist at NYULMC at screening. Exceptions to this eligibility include the following:
  - a. Any progressive glioma with *IDH1* or *IDH2* mutation, regardless of WHO grade, histopathological diagnosis, or prior therapy, will be eligible if the progressive tumor specimen is found to have one of the genetic alterations below:
    1.  $\geq 20$  somatic mutations per Mb by whole-exome sequencing
    2. High mutation burden or microsatellite instability (MSI) identified by Foundation Medicine panel next-generation sequencing (FoundationOne<sup>®</sup>, FoundationOne CDx<sup>™</sup>). Foundation Medicine's threshold for high mutation burden (HMB) in their panel NGS assays is  $\geq 20$  somatic mutations per Mb. Foundation Medicine's panel NGS assay has been validated by whole-exome and whole-genome sequencing to correlate tightly with tumor mutation burden ( $R^2 = 0.94$ ).<sup>96</sup>
    3. Mutation in a mismatch repair gene or other genes known to be associated with hypermutator phenotypes or microsatellite instability, including but not limited to *MSH2*, *MSH6*, *MLH1*, *POLE*, *PMS2*, *POLD* as determined by validated methods.
    4. Microsatellite instability as identified by polymerase chain reaction (PCR) or other validated methods.
  - b. Progressive oligodendroglioma (with 1p/19q codeletion) that has hallmark histopathological features of glioblastoma (i.e. necrosis, pseudopalisading necrosis, or microvascular proliferation) is eligible as *IDH1/2* mutant, 1p/19q codeleted oligodendrogliomas that have progressed after chemotherapy have been shown to develop hypermutation phenotype.<sup>32</sup>
5. Availability of a paraffin-embedded or frozen tumor-tissue block with a minimum of 1 cm<sup>2</sup> of tumor surface area from a tissue specimen that demonstrates pathological transformation to glioblastoma (WHO grade IV) or a progressive specimen that harbors one of the genetic alterations specified in Inclusion Criteria 4a.
  - a. If a tumor block cannot be submitted, then 20 unstained slides (preferably 10 slides from two different tumor blocks from the same surgery) from the tumor specimen must be submitted.
6. Patients must have had treatment with temozolomide, lomustine (CCNU) or PCV [procarbazine, lomustine (CCNU), vincristine] chemotherapy prior to histopathologic transformation to glioblastoma or prior to identification of one of the genetic alterations specified in Inclusion Criteria 4a. Notes or records from the treating oncologist are required for documentation of treatment history. Prior treatment with at least one of the following chemotherapy schedules is required to be eligible:
  - a. At least one 6 week course of continuous daily temozolomide

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- b. At least six 28-day cycles given in one of the following schedules:
    1. Daily for 5 days of a 28-day cycle
    2. Daily for 21 days of a 28-day cycle
    3. Daily for 14 days of a 28-day cycle
    4. Alternating 7 days on/7 days per 28-day cycle
    5. Continuous daily dosing of a 28-day cycle.
  - c. Other schedules of temozolomide may be considered after discussion with the overall Principal Investigator.
  - d. At least 3 cycles of PCV or lomustine (CCNU) chemotherapy.
7. Patients who received anti-tumor therapy after histopathologic transformation to glioblastoma must have shown unequivocal radiographic evidence of tumor progression by contrast-enhanced MRI scan (or CT scan if MRI is contraindicated).
8. Patients must have had prior CNS radiotherapy for their glioma, including standard doses for low-grade or high-grade glioma as well as non-standard dose and fractionation, including hypofractionated regimens, stereotactic radiosurgery, etc.
9. Patients can have had any number of prior therapies, including but not limited to molecularly targeted therapies and anti-angiogenic therapies, however they must have had prior chemotherapy with either temozolomide or lomustine as per Eligibility Criteria 6.
10. Karnofsky performance status (**Attachment 2**) of  $\geq 60$ .
11. Interval of at least 6 months from the completion of any prior radiotherapy and registration. If patients have not passed an interval of at least 6 months, they may still be eligible if they meet one or more of the following criteria:
  - a. New areas of tumor outside the original radiotherapy fields as determined by the investigator, or
  - b. Histologic confirmation of tumor through biopsy or resection, or
  - c. Nuclear medicine imaging, MR spectroscopy, or MR perfusion imaging consistent with true progressive disease, rather than pseudoprogression or radiation necrosis obtained within 28 days of registration AND an interval of at least 90 days between completion of radiotherapy and registration.
12. The following time periods must have elapsed prior to start of study treatment, the following time periods must have elapsed:
  - a. 5 half-lives from any investigational agent
  - b. 4 weeks from cytotoxic therapy (except 23 days for temozolomide and 6 weeks from nitrosoureas)
  - c. 6 weeks from antibodies
  - d. Prior treatment with other immune modulating agents within fewer than 4 weeks prior to the first dose of Avelumab.
    1. Examples of immune modulating agents include blockers of CTLA-4, 4-1BB (CD137), OX-40, therapeutic vaccines, or cytokine treatments.
  - e. 4 weeks (or 5 half-lives, whichever is shorter) from other anti-tumor therapies.
13. An interval of at least 2 weeks (to start of study agent) between prior surgical resection or one week for stereotactic biopsy.
14. Adequate hematologic, hepatic, and renal function defined by absolute neutrophil count  $\geq 1.5 \times 10^9/L$ , hemoglobin  $>9$  g/dL, platelet count  $\geq 100 \times 10^9/L$  (may have been transfused), aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5$  x upper limit of normal (ULN), total bilirubin  $\leq 1.5$  x ULN, and estimated creatinine clearance (CrCl)  $\geq 30$  mL/min according to the Cockcroft-Gault formula or local institutional standard method.
15. Women of child-bearing potential (WOCBP) and men able to father a child must agree to use highly effective contraception while on study drug and for 30 days after the last dose of

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Avelumab. WOCBP must have a negative pregnancy test within 28 days of initiation of dosing. Highly effective contraceptive measures include: stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomy and sexual abstinence.

- a. Contraception is not required for men with documented vasectomy.
  - b. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.
  - c. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
16. Willing to and capable of providing written informed consent prior to any study related procedures.
  17. Ability and willingness to comply with all study requirements, including scheduled visits, treatment plans, laboratory tests, and other study-related procedures.

## 4.2 Exclusion Criteria

1. Investigational drug use within 28 days of the first dose of Avelumab.
2. Planned participation in another study of an investigational agent or investigational device or use of a therapeutic device intended for therapy of glioma.
3. Prior therapy with an agent that blocks the PD-1/PD-L1 pathway.
4. Primary brainstem or spinal cord tumor.
5. Diffuse leptomeningeal disease at recurrence
6. Recurrent infratentorial tumor
7. Prior re-irradiation or stereotactic radiosurgery for recurrent disease at the same tumor location intended for HFRT in this study.
8. Maximal tumor diameter >4 cm
9. Patients with evidence of significant intracranial mass effect that requires >4 mg of dexamethasone or bioequivalent per day for 5 consecutive days for management of symptoms at any time within 14 days of registration.
  - a. Subjects on a standard high-dose steroid taper after craniotomy may receive a higher dose of corticosteroids within 14 days of registration, however must be at a dose  $\leq$ 4 mg of dexamethasone or bioequivalent per day within 5 days prior to registration.
  - b. Administration of steroids through a route known to result in a minimal systemic exposure [i.e., intranasal, intraocular, inhaled, topical, or local injection (e.g., intra-articular injection) corticosteroids (<5% of body surface area)] are permitted.
  - c. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are at doses  $\leq$  10 mg prednisone or bioequivalent per day.
  - d. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) are allowed.
10. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. The following are not exclusions:
  - a. Patients with diabetes type I, vitiligo, hypo- or hyperthyroid diseases, or psoriasis not requiring systemic immunosuppressive treatment are eligible.
11. Prior organ transplantation, including allogeneic stem cell transplantation.
12. Known history of, or any evidence of active, non-infectious pneumonitis within the last 5 years.
13. Known prior, severe hypersensitivity (NCI-CTCAE v4.03 Grade 3 or 4) to investigational product or any component in its formulations including known severe hypersensitivity reactions to monoclonal antibodies, any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more

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- features of partially controlled asthma).
14. Active infection requiring systemic therapy.
  15. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.
  16. Positive test for Hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus (HCV antibody) at screening indicating acute or chronic infection.
  17. Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
  18. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure ( $\geq$  New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
  19. Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia and sensory neuropathy Grade  $\leq$  2, or other Grade  $\leq$  2 not constituting a safety risk based on investigator's judgment, are acceptable.
  20. Patients with another active cancer [excluding basal cell carcinoma, cervical carcinoma in situ or melanoma in situ]. Prior history of other cancer is allowed, as long as there was no active disease within the prior 2 years.
  21. Pregnant or breastfeeding (negative serum or urine pregnancy test required for women of childbearing potential), or unable to maintain use of contraception while on study and for 30 days after the last dose of Avelumab.
  22. Known alcohol or drug abuse
  23. All other unstable, severe, or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
  24. Any condition that would prohibit the understanding or rendering of informed consent.

### **4.3 Subject Recruitment and Screening**

All efforts will be made to actively recruit and retain women and members of minority groups and their subpopulations in this study, with the objective of accruing a study population that resembles the age, gender, ethnic and racial composition of the adult U.S. population as closely as possible. The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of these populations. If any differences are observed in the outcomes of these populations, these results will be reported.

Patients will be recruited for the study from investigator or sub-investigator clinical practices. Screening requirements and diagnostic testing necessary to meet all inclusion and exclusion criteria (**Section 4.1 and Section 4.2**) are listed in detail in **Section 6.1**. Identification of prospective subjects will be conducted by reviewing the medical records of patients in the investigator or sub-investigator's clinical practice and the investigator and sub-investigators will use all efforts to limit its use of protected health information. For study requirements to maintain subject confidentiality and management of study information according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), refer to **Section 9.1** and **Section 9.2**.

Informed consent will take place in the investigator or sub-investigator's clinical practice per institutional guidelines when a patient is deemed potentially eligible for participation by the study investigator or sub-investigator. Patients will be asked to give medical information about themselves specific to the inclusion

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and exclusion criteria outlined in the protocol. Only study investigators will have access to this information. Information collected will include Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth), Parameters for eligibility, Parameters for exclusion, and Parameters for stratifications.

#### 4.3.1 **Informed Consent**

Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the research study and consent process. The participating investigator must assess the subject's capacity to provide informed consent to ensure subjects who lack capacity to provide informed consent are not enrolled. The assessment should include open-ended questions (i.e., not yes or no questions) regarding the purpose and involvement of the research. The investigator evaluating patient capacity must be an M.D. with experience in evaluating patient capacity. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients who are evaluated and/or treated by physicians in the oncology program will be given a consent form describing participation in the study. Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, nurse practitioner, or research nurse all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. For these patients, the consent letter and all other information will be administered orally and a witness, not related to the research project, will be present while the oral presentation is given. A short form will be utilized for the subject to sign in his/her name and the translator and/or witness must sign the short form. The translator will also sign the main consent form.

For patients who cannot read, a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

#### 4.3.2 **Documentation of Consent**

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

#### 4.3.3 **Multi-Site Surveillance**

As the lead investigator in a multi-site trial, the Overall Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's six month Data and Safety Monitoring report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's six month review to their IRB of record at the time of continuing review.

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#### 4.3.4 Patient Informed Consent at Additional Sites

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is NYULMC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials, unless Fellows are listed as co-investigators.

The Investigator must ensure that each participant is fully informed about the nature and objectives of the study and possible risks associated with participation. All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

All parties will ensure protection of participant personal data and will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, NYULMC Perlmutter Cancer Center (PCC) will maintain high standards of confidentiality and protection of participant personal data.

The informed consent form must be in compliance with ICH/GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and NYULMC before use.

### 4.4 Registration Procedures

#### 4.4.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULMC PCC Clinical Trials Office (CTO). The following materials must be submitted to the Research Coordinator for registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur within 24 hours of research coordinators' receipt of all the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be distributed to the study team upon registration.

Pretreatment evaluation will therefore be dictated by standard clinical practice. Eligible patients will be entered into the study by the study coordinator.

All patients will be required to sign a written informed consent prior to being registered on this study. Any patient not registered to the study before treatment begins will be considered ineligible and registration will be denied. Every effort will be made to answer questions raised by

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patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered on the study. Subjects must not start any protocol procedures prior to registration

Issues that would cause treatment delays should be discussed with the Overall Principal Investigator.

#### 4.4.2 Patient Registration at Other Participating Institutions

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is NYULMC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials.

Enrollment at additional sites can occur once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYULMC Perlmutter Cancer Center Clinical Trials Office. Once, all required documents are provided to NYULMC PCC Clinical Trials Office an activation notification will be sent to the PI and research coordinator at that site.

Central registration for this study will take place at NYULMC PCC.

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYULMC PCC Research Coordinator and forward a copy of the signed consent to NYULMC PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULMC PCC Clinical Trials Office. The following materials must be submitted to the Research Coordinator at NYULMC via email:

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur within 24 hours of research coordinators receipt of all of the above documents. Once eligibility is verified, a unique subject study number will be issued within 24 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYULMC PCC Clinical Trials Office will return a signed eligibility confirmation worksheet with the subject's unique study number. The subject will not be identified by name. This is the point, at which, the patient is considered on the study. Protocol treatment should begin within 5 days; issues that would cause treatment delays should be discussed with the overall PI, Sylvia Kurz, MD, PhD. Subjects must not start any protocol procedures prior to registration. Pretreatment evaluation will therefore be dictated by standard clinical practice.

Except in very unusual circumstances, each participating institution will order the study agent directly from the supplier.

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Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYULMC PCC Clinical Trials Office and to their IRB as per site institutional policy. See **Section 8.4** for detailed instructions on reporting requirements.

## **4.5 Early Withdrawal of Subjects**

### **4.5.1 When and How to Withdraw Subjects**

A subject has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion. The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for subject withdrawal from the study may include, but are not limited to:

- Subject withdrawal of consent at any time
- Disease progression
- Intolerable toxicity
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug.
- The investigator or sponsor determines it is in the best interest of the patient
- Failure of subject to adhere to protocol requirements (e.g., not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy
- Meeting of another study withdrawal criterion
- Study termination by Sponsor

Every effort should be made to obtain information on patients who withdraw from the study, including the reason for taking a participant off study. The date the participant was removed, must be documented. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

### **4.5.2 Data Collection and Follow-up for Withdrawn Subjects**

For End of Treatment required assessments see **Section 6 (Study Procedures)**, and **Schedule of Events (Attachment 1)**. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring and 90 days for serious adverse event reporting. Assessments may continue for ongoing reportable adverse events. A visit is to be performed at 30 days ( $\pm 7$  days) after the last study drug is given. Participants removed from protocol therapy for unacceptable adverse events will be following until resolution or stabilization of the adverse event.

Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for survival. After coming off study, each subject will be contacted every 3 months by telephone or medical record review to assess survival status until they meet criteria for removal from study as detailed below.

- Withdrawal of permission to record at least survival data
- Lost to follow-up
- Death

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If a subject withdraws permission to record at least survival data after coming off treatment, this must be documented along with the date the subject withdraws permission. Subjects will be considered lost to follow up if no medical records are available to be reviewed and two phone calls each to the subject and then the subject's next-of-kin (if the subject does not respond) are not returned over two consecutive 3 month periods.

## 5 Study Drug

### 5.1 Description

Avelumab (company code: MSB0010718C) is a fully human antibody (calculated molecular weight of 143,832 Dalton) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (IV) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of Avelumab.

Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. Avelumab drug product must be diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. It is recommended that the diluted avelumab solution is used immediately. Avelumab is administered as a 1-hour (-10/+20 minutes) IV infusion.

The **Pharmacy Manual** will be provided and contains specific instructions for Avelumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

### 5.2 Treatment Regimen

This is a multicenter, open-label, single-arm phase II trial of Avelumab in combination with hypofractionated radiation (HFRT) in adults with transformed *IDH* mutant GBM (for **Subject Selection Criteria** see **Section 4**; for **Study Schema**, see **Section 3.1.1**; for **Schedule of Events**, see **Attachment 1**; for details on **Radiation Treatment**, see **Attachment 6**).

An initial **Safety Lead-In** of 6 subjects will be conducted to define the safety and RP2D of Avelumab in combination with HFRT as detailed below in **Section 5.2.1**. The dose of Avelumab administered during the safety lead-in will initiate at the established phase II dose of Avelumab when administered as monotherapy (Dose Level 0). The safety lead-in also incorporates a de-escalation of Avelumab dosing if unexpected dose-limiting toxicity is observed in the first 6 subjects and follows a 3+3 phase I design as described below (**Section 5.2.1**). In the unlikely event that the Safety Lead-In phase of this study is unable to define an adequately safe dose of Avelumab administered with HFRT, the study will be stopped.

The RP2D of Avelumab administered with HFRT will be incorporated into the **Phase II portion** of this study.

**Avelumab** will be administered in an outpatient setting as an intravenous (IV) infusion; however, inpatient administration is permitted. Avelumab will be provided to patients enrolled on this study by EMD Serono/Merck KGaA.

**Pre-medication for Avelumab:** Subjects will receive Avelumab by IV infusion once every 2 weeks. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of Avelumab is mandatory prior to the first 4 infusions. Premedication should be administered for subsequent avelumab infusions based upon

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clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

**Infusion:** Avelumab is administered as a 1-hour (-10/+20 minutes) IV infusion. Each patient's dose will depend on individual body weight. The dose of Avelumab must be adjusted each dose for changes in body weight of  $\geq 10\%$ . Dose adjustments for changes in body weight of  $< 10\%$  will be at the discretion of the investigator. Following all avelumab infusions, subjects must be observed for 30 minutes post-infusion for potential infusion-related reactions. The **Pharmacy Manual** contains specific instructions for Avelumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

**Setting:** Avelumab should be administered in a setting that allows for immediate access to an environment that can immediately administer therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Planned Avelumab regimens to be assigned may include:

- 1 mg/kg IV infusion every 14 days for 2 years
- 3 mg/kg IV infusion every 14 days for 2 years
- 10 mg/kg IV infusion every 14 days for 2 years

After screening procedures and registration, all subjects will be treated with one dose of Avelumab IV at the assigned dose level. Study treatment should begin as close as possible to the date on which the participant is registered. One treatment cycle is defined as 28 days, corresponding to 2 doses of Avelumab. Avelumab will be administered every 14 days after the first Avelumab dose up to 3 days before or after the scheduled Day ( $\pm 3$ ) of each drug administration due to administrative reasons (i.e., Days  $1 \pm 3$  and  $15 \pm 3$  of a 28-day cycle).

All subjects will receive **hypofractionated radiation (HFRT)** to a total dose of 25 Gy given as 5 Gy per fraction over 5 consecutive fractions (for details on Radiation Therapy administration see **Attachment 6**). HFRT must begin 1 week after the first dose of Avelumab (i.e., Day 8 of Cycle 1). HFRT should preferably be given on consecutive days (i.e., Day 8 to Day 12).

Every attempt must be made to obtain the original radiotherapy treatment plan in order to guide re-irradiation treatment planning

All subjects will be evaluated every 8 weeks with radiographic imaging to assess response to treatment. The **Immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria (Attachment 3)**, which is based on the immune-related response criteria and the RANO criteria for brain tumor response assessment, will be used as the primary efficacy endpoint of PFS6.<sup>70</sup> Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI-CTCAE version 4.03.

Avelumab administration will continue for all subjects for 2 years or until the subject discontinues study therapy as per Subject Withdrawal guidelines, whichever comes first (**Section 4.5**). Subjects who are discontinued from study therapy will enter the post-study follow-up phase of the study as per **Section 4.5.2**.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

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### 5.2.1 Safety Lead-In

The study will initiate with a Safety Lead-In of 6 subjects. The first dose of study agent (Avelumab) will be administered after all procedures / assessments have been completed as detailed on the **Schedule of Events (Attachment 1)**. Avelumab will initially be administered at 10 mg/kg (IV) every 2 weeks (Dose Level 0, see **Table 1** below), which is the RP2D established for monotherapy administration (see section 1.4, Dose Rationale).

Beginning 7 days after the first dose of Avelumab (i.e. Day 8), all subjects will be administered HFRT to a total of 25 Gy, given in 5 fractions of 5 Gy on consecutive days (i.e., Day 8 to Day 12). Avelumab will continue to be given once every 2 weeks after the first Avelumab dose.

Once the initial 6 subjects are enrolled in the Safety Lead-In, enrollment will stop and subjects will be observed for 28 days for dose-limiting toxicities (DLTs, see **DLT definitions, Section 5.2.1.2**). At the end of the DLT period of 28 days, a **Safety Monitoring Team** consisting of the overall PI (Sylvia Kurz, MD, PhD), the Deputy Director of the Perlmutter Cancer Center who is not an investigator on the study, and the study biostatistician will review the safety data at a Safety Lead-In Dose Review meeting. This meeting will be led by the overall PI and at a minimum will be attended by the Safety Monitoring Team, the NYULMC Data Safety Monitoring Committee (DSMC), and a designated representative from each study site; other individuals, including sub-investigators, may be included. Continuation of enrollment will occur once all of the initial 6 subjects have completed the Day 28 safety assessments and the final dosing decision is made by the Safety Monitoring Team. However, screening for the next dose cohort may begin prior to confirmation that the current dose is safe.

The Safety Lead-In incorporates a de-escalation of Avelumab dosing if unexpected DLT is observed in the first 6 subjects. The Safety Monitoring Team and NYULMC DSMC will review the safety data at the end of the DLT period for the first 6 subjects and determine whether the study should proceed to phase II at Dose Level 0 or enter the dose de-escalation phase, which will follow a 3+3 phase I design. In the dose de-escalation phase, subjects will be enrolled and observed in groups of 3 for DLTs for an evaluation period of 28 days (see Dose De-Escalation Rules, **Section 5.2.1.1**, and **Study Schema, Section 3.1.1**). After 3 subjects are enrolled in each cohort, enrollment will stop and subjects will be observed for 28 days for DLTs. At the end of the DLT period, the Safety Monitoring Team and NYULMC DSMC will review the safety data at a Safety Lead-In Dose Review meeting that will include at least a representative from each site; sub-investigators may be included. Continuation of enrollment will occur once all 3 of the subjects have completed the Day 28 safety assessments and the final dosing decision is made by the Safety Monitoring Team. However, screening for the next dose cohort may begin prior to confirmation that the current dose is safe.

DLT will be determined by toxicities related to Avelumab during or beginning over the first 28 days of treatment as defined below in **Section 5.2.1.2 (Definition of DLT in for the Safety Lead-In)**. Subjects who experience DLT will be discontinued from study therapy and will enter the post-study follow-up phase of the study. Adverse events that meet DLT criteria but occur outside the DLT window will be classified as unacceptable AEs and study treatment will be discontinued.

Subjects are evaluable for DLTs if they have received at least one dose of Avelumab, have completed HFRT per protocol and have completed safety assessments over the entire DLT evaluation period (days 1 through 28). Any subject who discontinues treatment or withdraws from the study prior to completing the DLT evaluation period for any reason other than the occurrence of a protocol-defined DLT or other AE leading to study treatment discontinuation will be replaced (see also **Section 7.3.1**). Each replacement patient will be assigned a unique patient number, and will be treated at the same dose level as the replaced, prematurely withdrawn patient. Any patient who discontinues after the DLT observation period will not be replaced.

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Subjects who do not experience a DLT during the DLT period (28 days) and remain on study after the DLT period will continue Avelumab administration every 2 weeks for up to 2 years or until the subject discontinues study therapy as per Subject Withdrawal guidelines (**Section 4.5**). Subjects in the Safety Lead-In who are discontinued from study therapy may be considered for treatment resumption after resolution or stabilization of the condition if resuming treatment is thought to be in the best interest of the patient, however treatment may resume only after discussion with the Safety Monitoring Team, NYULMC DSMC and overall PI (see **Section 5.2.6.2**). Otherwise, all subjects who discontinue study therapy will enter the post-study follow-up phase of the study as per **Section 4.4.2**.

#### 5.2.1.1 Dose De-Escalation Rules

- If at **Dose Level 0**,  $\leq 1$  of the first 6 subjects develop DLT, the study will continue to phase II at Dose Level 0, which will be considered the **RP2D**.
- If at **Dose Level 0**,  $>1$  of the first 6 subjects develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 patients enrolled at Dose Level -1.
- If at **Dose Level -1**,  $\leq 1$  of the first 3 subjects develop DLT, 3 more subjects will be enrolled to Dose Level -1.
- If at **Dose Level -1**,  $\leq 1$  of the first 6 subjects develop DLT, the study will continue to phase II at Dose Level -1, which will be considered the **RP2D**.
- If at **Dose Level -1**,  $>1$  of the first 3 subjects develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 patients enrolled at Dose Level -2.
- If at **Dose Level -1**,  $>1$  of 6 subjects develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 patients enrolled at Dose Level -2.
- If at **Dose Level -2**,  $\leq 1$  of the first 3 subjects develop DLT, 3 more subjects will be enrolled to Dose Level -2.
- If at **Dose Level -2**,  $>1$  of the first 3 subjects develop DLT, the Safety Lead-In will be discontinued. In this case, the phase II portion of this study will not be conducted.
- If at **Dose Level -2**,  $\leq 1$  of the first 6 subjects develop DLT, the study will continue to phase II at Dose Level -2, which will be considered the **RP2D**.
- If at **Dose level -2**,  $>1$  of the first 6 subjects develops DLT, the Safety Lead-In will be discontinued. In this case, the phase II portion of this study will not be conducted.

**Table 1: Dose levels and doses to be evaluated in Safety Lead-In and for dose reductions**

<b>Dose Level</b>	<b>Avelumab Dose (mg/kg)</b>
Zero (0)	10 mg/kg
Minus one (-1)	3 mg/kg
Minus two (-2)	1 mg/kg

#### 5.2.1.2 Definition of Dose-Limiting Toxicity (DLT) for the Safety Lead-In

A DLT is defined as any grade  $\geq 3$  adverse event (AE) that is at least possibly, probably or definitely related to Avelumab or HFRT during the DLT period with the exceptions noted below.

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For guidance on assessing the relationship of AEs to Avelumab, HFRT, or study procedures, see **Attachment 5**. The sponsor may request information to justify the causality assessment of DLTs, as needed.

The DLT period is considered the first 28 days of study therapy, and will include labs and other evaluations taken at C1D28 (end of the first 28 days). The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays, will be analyzed to determine if a given toxicity should be considered a DLT for dose decision purposes. The final decision of whether or not the AE meets the DLT definition will be based on a careful review of all relevant data by the Safety Monitoring Team. The investigator may also be consulted.

In addition to the above, the following DLT exceptions will apply:

A DLT will be defined as any of the following:

- Grade  $\geq 2$  uveitis (considered as a potential **immune-related adverse event [irAEs** – see definition in **Section 5.2.3.3]**)
- Any Grade 4 AE **except** for single laboratory values out of normal range that are unlikely related to study treatment as described below in the DLT exceptions.

The following exceptions will **NOT** be classified as DLT:

- Grade 4 single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management
- Grade 3 **immune-related adverse events (irAEs** – see definition in **Section 5.2.3.3** and **Attachment 4**) other than uveitis that downgrade to Grade  $\leq 2$  within 14 days after onset of the event with maximal supportive care, including systemic corticosteroids.
- Grade 3 asymptomatic endocrinopathy, managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
- Grade  $\leq 3$  symptoms attributable to brain edema, per details in the **Rules for Brain Edema** below.
- Any pre-existing lab abnormality that deteriorates to Grade 3 or 4 that is considered unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolves within 7 days with adequate medical management.
- Transient ( $\leq 6$  hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient ( $\leq 24$  hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade  $\leq 1$ .
- Change in KPS to  $< 60$  that resolves to  $\geq 60$  within 14 days

While rules for adjudicating DLTs are specified above, an AE of Grade  $< 3$  (except if listed as exempt above), may also be defined as a DLT after a consultation with the overall study Principal Investigator, based on the emerging safety profile of Avelumab. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

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irAEs are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology (see **Section 5.2.3.3** and **Attachment 4** for Definitions and guidelines for management of irAEs).

Note: See **Section 8.1, Adverse Event Definitions**, for expected AEs related to Avelumab.

Note, any AE that meets DLT criteria will be considered an AESI and must be reported to the study sponsor (overall PI) within 24 hours of awareness of the event per **Section 8.3.1**. The study sponsor or designee will then notify the NYULMC PCC DSMC and IRB within 24 hours of awareness of the event.

**Rules for Brain Edema**: Development of edema in the brain is common following fractionated brain radiation therapy and may be asymptomatic (solely a radiographic finding) or associated with mild, moderate or severe symptoms. Therefore, brain edema will be considered an **expected** event related to study therapy (HFRT) and will **not** be considered a DLT unless brain edema meets CTCAE 4.03 criteria for "**Edema cerebral**" which only has a severity of Grade 4.

Note: **Grade 4 "Edema cerebral"** should only be used if the event meets CTCAE v4.03 criteria (i.e., Life-threatening consequences; urgent intervention indicated). Grade 4 Edema cerebral is considered a DLT and is defined by any of the following criteria:

- Any neurosurgical procedure is required to manage brain edema
- Requires an osmotic diuretic for management of symptomatic brain edema
- Requires >8 mg per day of dexamethasone or bioequivalent for more than 7 consecutive days to manage symptoms of brain edema
- Brain edema is deemed life-threatening per judgment of the treating investigator

Subjects who experience Edema cerebral Grade 4 will discontinue Avelumab immediately and will enter the post-study follow-up phase of the study. The overall PI may request additional information on events classified as Grade 4 cerebral edema.

For study purposes, the AEs deemed attributable to brain edema that do not meet Edema cerebral Grade 4 per CTCAE v4.03 should be described by the symptom (e.g. headache, nausea, focal neurological deficit) and graded for severity accordingly. If appropriate, the investigator should use the term "**Central nervous system necrosis**" per CTCAE 4.03 criteria if the investigator deems the radiographic findings are consistent with central nervous system radiation necrosis without symptomatic Grade 4 severity. Grade  $\leq 3$  AEs that are attributable brain edema or central nervous system necrosis will **not** be classified as DLT if:

- The grade 3 AE downgrades to Grade  $\leq 2$  within 7 days, or to Grade  $\leq 1$  or baseline within 14 days after onset of the event with maximal supportive care, including bevacizumab (see bevacizumab guidelines below) and/or systemic corticosteroid administration (no more than 7 consecutive days of dexamethasone dosed at >8 mg per day or bioequivalent).
- The grade 2 AE improves to grade  $\leq 1$  or baseline within 14 days after onset of the event with maximal supportive care, including bevacizumab and/or systemic corticosteroid administration (no more than 7 consecutive days of dexamethasone dosed at >8 mg per day or bioequivalent).

Note: For subjects who are suspected to have study treatment-related symptomatic intracranial or brain edema at any time during the study, Avelumab dosing should be

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immediately interrupted. **VEGF inhibition is preferred over corticosteroids** for management of suspected intracranial or brain edema, radiation necrosis, or intracranial hypertension, due to the risk that corticosteroids may suppress immune response against the tumor. Bevacizumab was granted accelerated approval by the US FDA for use as monotherapy in progressive GBM based on two historically-controlled, single-arm or non-comparative phase II trials however the addition of bevacizumab to standard of care in newly diagnosed GBM or to lomustine in recurrent GBM failed to show a benefit in overall survival in multi-institutional, randomized phase III trials.<sup>77,94,95</sup> Therefore, the addition of bevacizumab should not alter the survival outcomes of the study regimen. In addition, bevacizumab has been reported to be safe in combination with anti-PD-1/PD-L1 pathway inhibitors and re-irradiation to 30 Gy in a phase I trial of recurrent GBM patients,<sup>62</sup> and the combination of bevacizumab with anti-PD-1/PD-L1 pathway inhibitors is being investigated in a number of clinical trials, including for gliomas.

The VEGF inhibition strategy will be **bevacizumab (at a maximal dose of 10 mg/kg IV) every 2 weeks, for a minimum of 2 doses**. If VEGF inhibition does not resolve the symptoms to grade  $\leq 1$  or baseline, the investigator may institute systemic corticosteroids, in addition to or as a replacement for bevacizumab, at the lowest dose that is appropriate for symptom management.

If the symptoms improve to grade  $\leq 1$  or baseline by 2 weeks after the last dose of Avelumab, the subject may stop bevacizumab and continue Avelumab on study. If symptoms do not improve to grade  $\leq 1$  or baseline by 2 weeks after the last dose of Avelumab, the subject must permanently discontinue study treatment. If a subject requires a neurosurgical procedure or mannitol to manage grade  $\geq 3$  symptom attributable to intracranial or brain edema, the AE will be considered a DLT and the subject must permanently discontinue study treatment.

Note: Any AE of grade 3 or greater that is suspected to be attributable to brain edema will be considered an AESI and must be reported to the study sponsor (overall PI) within 24 hours of awareness of the event per **Section 8.3.1**. The study sponsor or designee will then notify the NYU DSMC and IRB within 24 hours of awareness of the event.

Note: Immune cell infiltration may be associated with increasing enhancement and edema on brain MRI or CT (i.e. pseudoprogression) and may mimic therapy-related central nervous system radiation necrosis or disease progression. Due to the well-described difficulty in differentiating between immune-mediated pseudoprogression and true tumor progression using standard imaging techniques,<sup>72</sup> particularly in brain tumors,<sup>70</sup> special attention must be made to events that are suspected to be attributed to possible brain edema and central nervous system necrosis.

For guidelines on managing radiographic findings, refer to **Section 6.7, Efficacy Procedures** and **Attachment 3, iRANO** criteria. A symptom or AE is initially suspected to be due to pseudoprogression or central nervous system necrosis may be later considered to be due to **disease progression** after review of additional imaging, biopsies and consultations with the treating investigators by the Safety Monitoring Team. These events may be reviewed for dosing decisions during the Safety Lead-In and toxicity monitoring during the phase II trial.

## 5.2.2 Phase II Trial

Following determination of the RP2D for Avelumab when combined with HFRT in the Safety Lead-In, subjects meeting eligibility criteria will receive Avelumab administered intravenously at the RP2D. A total of 43 patients are anticipated to be treated in the Phase II trial. The Phase II trial is a two stage design phase II trial with a planned interim analysis for futility and planned interim analyses for safety (see **Section 7.2.2** for **Statistical Methods**).

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The first dose of study agent (Avelumab) will be administered after all procedures / assessments have been completed as detailed on the Schedule of Events (**Attachment 1**). Avelumab will be administered IV at the RP2D established for administration with HFRT in the Safety Lead-In.

Beginning 7 days after the first dose of Avelumab (i.e. Day 8), all subjects will be administered HFRT to a total of 25 Gy, given in 5 fractions of 5 Gy on consecutive days (i.e., Day 8 to Day 12).

After the first dose, Avelumab administration will continue every 2 weeks. Avelumab administration will continue for up to 2 years or until the subject discontinues study therapy as per **Subject Withdrawal** guidelines (**Section 4.5**). Subjects who are discontinued from study therapy will enter the post-study follow-up phase of the study as per **Section 4.5.2**.

## 5.2.3 Dose Modification and Study Treatment Discontinuation Rules

### 5.2.3.1 Avelumab Dose Modification

Once the RP2D is established in the Safety Lead-In portion of the study, no dose reductions of Avelumab will be allowed. During the Safety Lead-in portion of the study, dose reductions for an individual subject will not be allowed.

### 5.2.3.2 Avelumab Hold or Discontinuation

Safety Lead-In: All subjects who experience protocol-defined DLTs (either during or outside the DLT observation period) during the Safety Lead-In will be required to discontinue treatment with Avelumab. In addition, treatment hold and discontinuation guidelines are provided below.

For all subjects:

Note: For additional information regarding AEs with a potential immune etiology (**irAEs**), see **Section 5.2.3.3, Table 3 and Attachment 4**.

**Attachment 4** includes guidelines on the **management of specific treatment-related AEs and when to delay and/or discontinue Avelumab**. These guidelines are intended to be applied when the investigator determines the events to be treatment-related.

Note: Infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), should be handled according to guidelines in **Section 5.2.3.5**.

Note: See **Section 8.1, Adverse Event Definitions**, for expected AEs related to Avelumab. Brain edema is an expected AE related to HFRT.

**No Avelumab dose reductions are permitted.**

If Avelumab is temporarily withheld, the cycle count should be interrupted. Subjects who experience an adverse event that requires a treatment delay should be monitored with appropriate laboratory testing or other clinical evaluation at least weekly until resolution.

If Avelumab is discontinued (either permanently or temporarily) for an AE, the subject will generally discontinue the combination therapy treatment (HFRT) as well. If, however, a subject experiences an AE that in the opinion of the investigator is SOLELY related to HFRT, Avelumab may be continued and HFRT may be discontinued as per **Section 5.2.3.4**. Conversely, if a subject experiences an AE that in the opinion of the investigator is SOLELY related to Avelumab, then HFRT may be continued while Avelumab may be discontinued as per **Section 5.2.3.2**.

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**Table 2: Guidelines for Avelumab Hold and/or Discontinuations for Symptoms Related to Brain Edema or Central Nervous System Necrosis**

Grade	Hold Avelumab?	Restarting Criteria	Discontinuation Criteria
1	No	N/A	N/A
2	Consider withholding for persistent symptoms Consider bevacizumab if symptoms persist <sup>1</sup>	Toxicity resolves to Grade 0–1 or baseline	Toxicity does not resolve to Grade 0–1 or baseline within 14 days of last infusion or requires >8 mg/day of dexamethasone or bioequivalent for >7 consecutive days to treat symptoms
3	Yes Initiate bevacizumab in addition to appropriate symptomatic treatment <sup>1</sup>	Toxicity resolves to Grade 0–1 or baseline	Toxicity does not resolve to Grade ≤2 within 7 days, or to Grade ≤1 or baseline within 14 days of last infusion, or requires >8 mg/day of dexamethasone or bioequivalent for >7 consecutive days to treat symptoms
4 <sup>2</sup>	Yes	N/A	Patient must be discontinued

**Note:** Per CTCAE v4.03, the AE "**Edema cerebral**" only has Grade 4 severity. The AE "Edema cerebral" should be used only if the symptom severity meets the CTCAE v4.03 criteria (i.e., "Life-threatening consequences; urgent intervention indicated"). See **Rules for Brain Edema, Section 5.2.1.2**

<sup>1</sup> For subjects who develop symptoms of **Grade ≤3** attributable to **brain edema** or **central nervous system necrosis**, maximal supportive care and symptomatic treatment, including bevacizumab and/or systemic corticosteroids, should be administered as clinically appropriate. **Bevacizumab is preferred over corticosteroids** for management of suspected intracranial or brain edema, radiation necrosis, or intracranial hypertension, due to the risk that corticosteroids may suppress immune response against the tumor. Bevacizumab should be given at a maximal dose of 10 mg/kg IV every 2 weeks, for a minimum of 2 doses. If bevacizumab does not resolve the symptoms to grade ≤ 1 or baseline, the investigator may institute systemic corticosteroids, in addition to or as a replacement for bevacizumab, at the lowest dose that is appropriate for symptom management in order to avoid significant immunosuppression. Corticosteroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks if doses >4 mg/day of dexamethasone or bioequivalent are administered for >7 days. See **Rules for Brain Edema** in **Section 5.2.1.2** for guidance of AE classification and management.

<sup>2</sup> Subjects who experience **Edema cerebral, Grade 4** per CTCAE v4.03 criteria, must discontinue Avelumab. For study criteria that qualify for Grade 4 Edema cerebral see **Rules for Brain Edema** in **Section 5.2.1.2**.

### 5.2.3.3 Immune-related adverse events (irAEs)

Special attention should be paid to AEs that may be suggestive of a potential immune-mediated pathophysiology (irAEs), defined as AEs of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE v4.03 Grade).

An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the overall Principal Investigator.

**General recommendations for symptomatic management of irAEs include the following:**

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- Grade 1 to 2: Treat symptomatically or with moderate dose corticosteroids, more frequent monitoring
- Grade 1 to 2 (persistent): Manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: Treat with high dose corticosteroids

Treatment of gastrointestinal, dermatological, pulmonary, hepatic and endocrine irAEs should follow guidelines set forth in **Attachment 4 (Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific Drug-Related Adverse Events)**.

Note: Any irAE of grade 3 or greater will be considered an AESI and must be reported to the study **sponsor** within 24 hours of awareness of the event per **Section 8.3.1**. AESIs should be reported to the local institution's DSMC and IRB per local institution guidelines. If the AESI is **not** a DLT or SAE, there is no need to report to the DSMC or IRB within 24 hours unless specified by the local institution's DSMC or IRB.

**Table 3** includes **general guidelines for managing irAEs**. **Attachment 4** includes recommendations on the management of specific treatment-related irAEs and when to delay and/or discontinue Avelumab. These guidelines are intended to be applied when the investigator determines the events to be treatment-related.

**Table 3: General Treatment Hold Guidelines for Immune-Related Adverse Events (irAEs)**

Severity	Withhold/ Discontinue Avelumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold Avelumab at the treating investigator's discretion	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3	Withhold Avelumab  Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone or bioequivalent within 4 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 0.5 to 1.0 mg/kg/day methylprednisolone or bioequivalent.  Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.
Grade 4*	Discontinue Avelumab	Discontinue Avelumab

Note: These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Note: For guidelines regarding **specific AEs** with a potential immune etiology (irAEs), reference **Attachment 4**. For any AE that is of a type known to be potentially immune-related (e.g., rash, colitis, transaminitis, endocrine), but is deemed not to be an irAE by the investigator, the overall PI may request additional information.

Note: During the **Safety Lead-In**, depending on the nature of AE, for subjects who develop Grade 2 irAE, Avelumab will be held if symptoms do not improve to grade ≤1 with appropriate supportive care and symptomatic treatment within 14 days after onset of the event and will be considered DLT. See **Section 5.2.1.2** for **DLT definitions**.

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**Note:** During the **Safety Lead-In**, for subjects who develop Grade 3 irAE, Avelumab will be held and will be considered at DLT if symptoms do not improve to grade  $\leq 2$  within 14 days after onset of the event with appropriate supportive care and symptomatic treatment. See **Section 5.2.1.2** and **Attachment 4**.

\* For Grade 4 amylase and lipase elevations, follow guidelines for Grade 3 irAE. Avelumab only requires permanent discontinuation for Grade 4 amylase and lipase elevations if the corticosteroid dose cannot be reduced to  $< 10$  mg day prednisone or bioequivalent within 4 weeks of toxicity.

#### 5.2.3.4 Hold of Hypofractionated Radiation Therapy (HFRT)

Radiation therapy will be held for Grade 3 or higher radiation therapy-related, nonhematologic toxicity. Radiation therapy will resume at the discretion of the investigator at full dose when toxicity returns to Grade 1 or 0.

In addition, though development of symptomatic brain edema during the actual period of radiation treatment is unlikely, radiation therapy for any patient experiencing grade 3 or higher symptoms related to brain edema prior to completing radiation treatment should be put on hold until symptoms resolve and the case is clinically evaluated. See **Table 2** in **Section 5.2.3.2** and **Rules for Brain Edema** in **Section 5.2.1.2** for detailed instructions regarding management of radiation therapy-related brain edema.

#### 5.2.3.5 Management of Infusion/Allergic/Hypersensitivity Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (e.g., antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs (**Section 8**) and graded according to the NCI-CTCAE version 4.03 grading scale (**Section 8**).

Signs/symptoms may include:

- Fever
- Chills
- Rigors
- Diaphoresis (sweating)
- Headache

**Table 4 - Modification of Avelumab Infusion for Symptoms of Infusion-Related Reactions**

NCI-CTCAE Grade	Treatment Modification for Study Drug
<b>Grade 1 – mild</b> Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the Avelumab infusion rate by 50% and monitor closely for any worsening.
<b>Grade 2 – moderate</b> Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for $\leq 24$ h.	Temporarily discontinue Avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
<b>Grade 3 or Grade 4 – severe or life-threatening</b> <b>Grade 3:</b> Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization	Stop the Avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from Avelumab treatment and must not receive any further Avelumab treatment.

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indicated for clinical sequelae. <b>Grade 4:</b> Life-threatening consequences; urgent intervention indicated.	
<p>- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.</p> <p>- If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.</p>	

IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction Grade  $\geq 2$  on the slower infusion rate, the infusion should be stopped and the subject should be removed from study treatment. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue study drug.

### Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the Investigator.

**Note:** Grade 2 or greater infusion-related reactions or Grade 2 or greater allergic/hypersensitivity reactions will be considered an AESI and must be reported to the study sponsor within 24 hours of awareness of the event per **Section 8.3.1**. AESIs should be reported to the local institution's DSMC and IRB per local institution guidelines. If the AESI is **not** a DLT or SAE, there is no need to report to the DSMC or IRB within 24 hours unless specified by the local institution's DSMC or IRB.

### Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

### Termination of the Infusion

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The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis laryngeal/pharyngeal edema severe bronchospasm
- chest pain
- seizure
- severe hypotension

#### 5.2.3.6 Note on continuation of therapy pending confirmation of radiographic disease progression

Immunotherapy response criteria in neuro-oncology (iRANO) criteria (**Attachment 3**), which is used in this study for efficacy evaluation, recommends confirmation of disease progression on follow-up imaging 3 months after initial radiographic progression if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy. A decision of whether a patient should continue immunotherapy pending confirmation of radiographic disease progression should be established based on perceived benefits and risks. Continuation of immunotherapy may be considered pending follow-up imaging as long as subjects are deriving apparent clinical benefit with minimal and acceptable toxic effects. See **Attachment 3** and **Section 6.7, Efficacy Procedures**, for further details.

#### 5.2.3.7 Permanent Discontinuation of Study Treatment

In the event of an infusion reaction of Grade  $\geq 3$  severity during or directly following Avelumab infusion, dosing should be stopped and the patient must permanently discontinue Avelumab treatment.

Study treatment will be permanently stopped in the event of evidence of pregnancy.

In addition, study treatment for any subject may be discontinued for other safety reasons or compliance issues at the discretion of the investigator, overall PI or sponsor. A subject may choose to discontinue study treatment or study participation at any time for any reason.

A subject who permanently discontinues Avelumab treatment may continue follow-up in the study without additional treatment until progression of disease or closure of the study (**Section 4.5**). A patient who permanently discontinues study treatment and who does not withdraw from study participation will be asked to return to the clinic for all remaining study visits per the visit schedule (**Attachment 1**) or continue in the follow-up phase of the study until progression of disease or closure of the study (**Section 4.5.2**).

### 5.3 Preparation and Administration of Study Drug

Avelumab will be prepared in the site investigational pharmacy. Preparation of the diluted Avelumab for administration must be accomplished by adequate trained personnel to guarantee the sterility of the product to be injected. Only clinical site personnel who are appropriately trained on the procedure detailed in this document may perform the preparation and administration procedures specified in this manual. Clinical site personnel involved in these procedures must comply with all applicable regulations and standards. The administration must be performed by adequately trained personnel. Prior to dosing the subject, adhere to normal standard of care and aseptic techniques. Utilize local site procedures as appropriate. See **Section 1.2.4** for specific Avelumab handling instructions and refer to the **Pharmacy Manual** for complete instructions for Avelumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

#### General Preparation Instructions:

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To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel under a laminar flow box using aseptic techniques.

Avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used only if the first option is not applicable. The verified Avelumab concentration range in the infusion solution is 0.016 mg/mL to 8 mg/mL.

- Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature.
- Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by Avelumab from the infusion bag and discard the removed solution.
- Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag.
- Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution.
- The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

**No other drugs should be added to the solution for infusion containing Avelumab.**

Prepared solution for dosing should be kept at room temperature and used immediately after preparation. The chemical and physical in-use stability for the infusion solution of Avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user.

#### **General Administration Instructions:**

The administration must be performed by adequately trained personnel. Prior to dosing the subject, adhere to normal standard of care and aseptic techniques.

- The prepared Avelumab dosing solution for infusion is connected to the infusion set equipped with a 0.2 micron PES (or PSU but only if PES membrane is not available) in-line filter and an appropriate gauge standard venous catheter for the subject. Alternatively, a permanent venous catheter or implantable port may be used. Prior to infusion, prime the assembly with the dosing solution.
- Set the infusion pump to deliver the entire infusion volume over 1 hour (-10/+20 minutes). A constant infusion rate is achieved by using a microprocessor-controlled infusion pump.
- Immediately following the infusion of Avelumab, it is recommended (but not mandatory) to conduct a normal saline flush using the same tubing and 25-100 mL normal saline infused at the same rate to clear the infusion set of residual drug.

#### **Special Precautions for Avelumab administration:**

Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000

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dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

**Observation period:** Following all avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration are provided in the **Pharmacy Manual**. For detailed information on the assigned dose levels and the concrete volumes to be replaced to prepare the target doses, please refer to the **Pharmacy Manual**.

#### **5.4 Subject Compliance Monitoring**

Avelumab and radiation treatments will be administered at the study site and recorded on the case report form (CRF) and captured in Velos. All dosing records for each patient will be kept by the site. Patients will be administered IV Avelumab in a clinic or hospital setting under supervision of appropriate study personnel. Radiation therapy will be administered at the study site.

Subjects who are significantly non-compliant (e.g., not complying with protocol required visits, assessments, and dosing instructions) may be withdrawn from the study by the investigator and/or sponsor. The investigator and/or sponsor have the right to discontinue a subject from study treatment or withdraw a patient from the study at any time.

All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

#### **5.5 Prior and Concomitant Therapy**

Avelumab, as a mAb, is not expected to have a direct drug-drug interaction (DDI) effect on other small molecule drugs. In addition, like other immune checkpoint inhibitors in the class, Avelumab is not considered to be a cytokine modulator, which was confirmed by cytokine data collected from EMR 1000700-001 (see Investigator's Brochure). In summary, Avelumab is not expected to have DDI with other drugs because it is primarily metabolized through catabolic pathways and is not expected to affect the expression of CYP450 enzymes.

##### **5.5.1 Concomitant Medications**

Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the 5 month follow-up period to treat a study-drug-related AE.

All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

##### **5.5.2 Acceptable Concomitant Medications**

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Physiologic replacement doses of systemic corticosteroids are permitted after consultation with the overall PI or designee, even if >10 mg/day prednisone equivalents. Standard doses of hydrocortisone for maintenance therapy are 10–20 mg/m<sup>2</sup>/day divided 2–4 times per day. For a subject with a body surface area (BSA) of 1.73 m<sup>2</sup>, this translates to a total dose of 34.6 mg of

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hydrocortisone per day. The equivalent dose of dexamethasone is 1.2 mg per day. Some subjects may additionally receive mineralocorticoid-replacement maintenance therapy with fludrocortisone. The maintenance dose of fludrocortisone for this indication is 0.05–0.1 mg/day.

Intranasal, inhaled or topical corticosteroids (<5% of body surface area) for the treatment of mild/moderate asthma, allergies or dermatitis are permitted. Antihistamines and other non-steroidal anti-allergy medications are also permitted. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

During the study, bevacizumab is permitted and preferred over corticosteroids for management of symptoms related to intracranial/brain edema or central nervous system radiation necrosis. See **Rules for Brain Edema** in **Section 5.2.1.2** for guidelines on management of symptoms related to intracranial/brain edema, bevacizumab administration, and corticosteroid use in this setting.

### 5.5.3 Prohibited Medications

Medications or vaccinations specifically prohibited in the **Exclusion Criteria (Section 4.2)** are not allowed during the ongoing trial except as outlined below. While participating in this study, a patient may not receive any standard or investigational agent or device for treatment of a tumor other than Avelumab in combination with radiation therapy per the study's specified dosing regimens.

It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) at any time throughout the study except in the cases of physiologic replacement, supportive post-operative management, a life-threatening emergency, to treat an irAE or suspected irAE, or to treat symptomatic brain edema or radiation necrosis. For guidance on systemic corticosteroid administration for symptomatic brain edema or radiation necrosis, See **Rules for Brain Edema** in **Section 5.2.1.2** and **Table 2** in **Section 5.2.3.2**.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The treating investigator should discuss any questions regarding this with the overall study PI or his designee. The final decision on any supportive therapy or vaccination rests with the treating investigator. However, the decision to continue the subject on trial therapy requires the mutual agreement of the Investigator, overall study PI or his designee, and the subject.

## 5.6 Packaging

Avelumab study agent will be packaged in a carton box labeled and tamper sealed containing a PET tray and 8 labeled vials. Each single-use 10 mL vial contains 200 mg of Avelumab (20 mg/mL).

Study drug boxes consist of:  
Inserts for folding box (PET tray)  
Tamper Seal

Label Example:

<u>Phase</u>	<u>Label description</u>
II	Vial & Box Single Panel Labels

Master Label text in English according to US regulations

US Vial Master Label Text:

1. EMD Serono/Merck assigned protocol number

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2. MSB0010718C (drug name)
3. 200 mg (dose strength)
4. 10 mL per vial
5. 20 mg/mL
6. XXXXXXX (Medication no.)
7. Sponsor information
8. XXXXXXX (Lot no.)

Concentrate for solution for intravenous infusion

Caution: New Drug! Limited by Federal (or United States) law to investigational use

Supplied by Merck KGaA, Darmstadt, Germany

US Box Master Label Text:

1. EMD Serono/Merck assigned protocol number
2. MSB0010718C (drug name)
3. 200 mg (dose strength)
4. 10 mL per vial
5. 20 mg/mL
6. 8 (Quantity of vials)
7. 36-46°/ 2-8°(Storage Conditions F/ °C)
8. Space for Subject Number to be written in by site
9. Space for Investigator to be written in by site
10. Sponsor
11. XXXXXXX (Medication no.)
12. XXXXXXX (Lot no.)

Concentrate for solution for intravenous infusion

Use according to handling instruction

For clinical trial use only!

Keep out of reach of children

Store all items in original outer packaging, remove only prior to administration

Do not freeze

Do not shake

Protect from light

Caution: New Drug! Limited by Federal (or United States) law to investigational use

Supplied by Merck KGaA, Darmstadt, Germany

## **5.7 Receiving, Storage, Dispensing and Return**

### **5.7.1 Receipt of Drug Supplies**

EMD Serono/Merck KGaA will package and distribute the study drug to sites via their distribution vendor - Fisher Clinical Services. The study drug will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices. The study drug will be shipped to the investigational pharmacy at each site.

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

### **5.7.2 Storage**

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See **Section 1.2.3** for Instructions for storage and **Section 1.2.4** for special instructions for handling.

### 5.7.3 Dispensing of Study Drug

The NYU Investigational pharmacist or their designee pharmacist or other qualified individual will be identified at each site to prepare Avelumab for administration. Refer to **Section 5.3** for Avelumab administration instructions.

All drug accountability records must be kept current. The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee. All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

### 5.7.4 Return or Destruction of Study Drug

#### Retention of Drug Product Vials:

All opened vials (full, partially full, and empty) may be destroyed at the site by the appropriate site personnel (e.g., pharmacist, study nurse/coordinator) following local environmental requirements and institutional policies. All destruction must be fully documented at the time of destruction on the investigational product accountability log, or equivalent document at the time of destruction.

If opened vials are not destroyed immediately following drug preparation, opened vials must be stored in sealed, clear plastic bags until destruction.

**All unopened vials must be destroyed at the end of the treatment period unless EMD Serono/Merck KGaA provides separate instructions for return.**

#### Retention of supplies:

Normal saline solution may be disposed of according to local site procedures. Other items used in the dose preparation and administration should be disposed of according to local site procedures.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. All unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Drug destroyed on site will be documented in the study files.

## 6 Study Procedures

### 6.1 Screening Procedures

After providing informed consent, patients will undergo screening for eligibility to participate in the study. Screening will start within 21 days prior to initiation of study treatment (first dose of Avelumab). Refer also to the **Schedule of Events (Attachment 1)** for complete details of study procedures.

The following procedures will be performed at **Screening** for the purpose of determining study eligibility or characterizing the baseline population:

- Documentation of an *IDH1* or *IDH2* mutation on any tumor specimen must be confirmed

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- Diagnosis (pathology report is sufficient) of WHO grade II or III glioma prior to therapy with temozolomide or PCV must be confirmed.
- The tumor specimen that has progressed after treatment with temozolomide, lomustine, or PCV (per Section 4.1, Inclusion Criteria 6) must have histopathologic diagnosis of transformation to glioblastoma (WHO Grade IV). Central review of the glioblastoma diagnosis in the progressive tumor specimen is required prior to registration.

At least one (1) H&E slide that demonstrates the diagnosis of glioblastoma, WHO grade IV, and that is representative of the required archival tissue to be submitted is sufficient for central review. A recut slide is acceptable if the original clinical diagnostic slides cannot be sent. For the central review confirmation, there is no minimal tumor content required as long as the slide demonstrates characteristics satisfying WHO criteria for glioblastoma (grade IV).

The diagnostic pathology slide(s) from the glioblastoma (WHO Grade IV) tumor specimen must be submitted to NYULMC at screening for central review confirmation prior to registration.

Send diagnostic pathology slides for central review to:

Matija Snuderl, MD  
Department of Pathology, NYU Langone Medical Center  
560 First Avenue  
Tisch Hospital HW 451  
New York, NY 10016  
Phone: 646-501-5281  
Fax: 212-263-7916  
Pager: 917-205-5543  
Matija.Snuderl@nyumc.org

**Exception Note:** Any progressive glioma with *IDH1* or *IDH2* mutation, regardless of WHO grade, histopathological diagnosis, or prior therapy, will be eligible if the progressive tumor specimen is found to have one of the genetic alterations associated with hypermutation phenotype per **Section 4.1, Inclusion Criteria 4a**. A molecular pathology report indicating an eligible genetic alteration is sufficient documentation for an eligible genetic alteration and central histopathologic review is not needed for this exception.

- Collection of archived tumor material for research: The subject will be asked to arrange to provide archival tumor tissue from a surgical resection that demonstrates histopathological evidence of glioblastoma (GBM, WHO grade IV) or a genetic alteration as specified in the **Eligibility Criteria (Section 4.1)**.
- Brain MRI (or CT if MRI is contraindicated): Contrast-enhanced brain MRI or CT must be performed within 14 days prior to the first dose of study treatment (Avelumab infusion)
- Medical history: The subject must be eligible by all of the **Subject Selection Criteria** per **Section 4**. Concomitant therapeutics will be reviewed for allowed or prohibited medications. Of note:
  - Subjects must have documentation (treating oncologist note or treatment summary) of treatment with temozolomide, CCNU or PCV chemotherapy for their glioma prior to the transformation to GBM as specified in the **Eligibility Criteria (Section 4.1)**.
  - Subjects who received anti-tumor therapy after histopathologic transformation to glioblastoma must have shown unequivocal radiographic evidence of tumor progression by contrast-enhanced MRI scan (or CT scan if MRI is contraindicated).

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- Chest x-ray: Chest x-ray is required at screening if not performed within 60 days prior to initiation of study treatment.
  - Note: Baseline chest x-ray is required as this may assist in subsequent clinical assessments that may occur during the study. For example, in a circumstance in which a patient presents to a provider with signs and symptoms that may be related to a pulmonary process, standard clinical practice often is to obtain a chest x-ray. In order to interpret a chest x-ray in this situation, it is clinically helpful to have a recent baseline chest x-ray on file. Hence, a baseline chest x-ray is required if not performed in the prior 60 days. In the absence of a baseline chest x-ray, the most recent chest imaging would be a CT scan of the chest, which could lead to the clinical decision to obtain another CT scan of the chest in clinical circumstances in which a chest x-ray would have been sufficient.
- 12-Lead ECG: A standard 12-lead ECG will be required only at screening. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator if needed. Any ECG finding performed during the study period after screening that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored. The following will be recorded on the CRF:
  - PR Interval (msec)
  - QRS Interval (msec)
  - QT Interval (msec)
  - Heart Rate (BPM; recorded from the ventricular rate).
- Physical exam and laboratories: Subjects will have the following vital signs, physical exam and laboratory procedures evaluated for eligibility if not already performed within 21 days prior to initiation of study treatment (first dose of Avelumab). For complete details see the **Schedule of Events (Attachment 1)**.
  - Complete physical exam, including neurological exam, and KPS assessment
  - Vital signs: height (height is only required at screening), weight, temperature, resting blood pressure, pulse and respiration rate.
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
  - Urinalysis: glucose, blood, pH, specific gravity, ketones, and urine protein
  - Coagulation test (required at screening only): PT/INR, PT, PTT
  - Thyroid stimulating hormone (TSH), free T4
  - Hepatitis B virus surface antibody, hepatitis B virus surface antigen, hepatitis B virus core antibody, and hepatitis C virus antibody
  - Pregnancy test (Urine or serum  $\beta$ -HCG) for women of child-bearing potential

## 6.2 Cycle 1, Day 1 (C1D1)

After screening and registration, all patients will have the C1D1 Safety Procedures detailed below within 3 days of treatment initiation (first dose of Avelumab). Evaluations performed at screening that fall within 3 days of treatment initiation will not need to be repeated.

- Adverse event assessment

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- Complete physical exam, including neurological exam, and KPS assessment
- Vital signs: When scheduled at the same visit as other procedures, vital signs should be measured prior to clinical laboratory assessments or research blood sample collection.
  - Weight (can be taken within 3 days of scheduled Avelumab administration)
  - For C1D1, the following vital signs will be collected prior to treatment, at the end of the infusion, and 30 minutes post-infusion (all infusion VS timepoints  $\pm 10$  minutes):
    - Temperature, resting blood pressure, pulse and respiration rate.
    - Note: following all Avelumab infusions, subjects must be observed for 30 minutes post-infusion for potential infusion-related reactions.
- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH)
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
- Thyroid stimulating hormone (TSH), free T4
- Pregnancy test (urine or serum  $\beta$ -HCG) for women of child-bearing potential
- Research blood samples. All subjects will have the below research blood samples collected. *Note:* Research blood samples will be taken at only 2 timepoints: **C1D1 (pre-dose)** and **C2D1**. For details on Background and Rationale of research studies, see **Attachment 7**. For details on specimen collection, processing, handling and shipping, refer to **Section 6.8** and the study **Lab Manual**.
  - NYULMC subjects: 40 mL (four 10 mL purple top EDTA tubes) of whole blood will be drawn and immediately sent to the below sites:
    - One (1) 10 mL tube will be sent to the Center for Biospecimen Research and Development (CBRD) at NYULMC for acquisition of whole blood, buffy coat, and plasma samples.
    - Three (3) 10 mL tubes will be sent to the Immune Monitoring Core (IMC) at NYULMC and immediately processed for isolation of PBMCs.
  - Subjects at other sites: 40 mL of whole blood will be collected in two types of tubes provided by NYULMC. All tubes will be shipped overnight to the CBRD at NYULMC per instructions in the **Lab Manual**.
    - 10 mL will be drawn into one Streck Cell-Free DNA BCT® collection tube.
    - 30 mL total will be drawn into three 10 mL purple top EDTA tubes and immediately sent to NYULMC.

Avelumab will be administered IV at the specified dose level in the Safety Lead-In or the RP2D for the phase II trial (for details see **Treatment Regimen, Section 5.2**). The day of the first Avelumab infusion will be designated as Cycle 1, Day 1. Each patient's dose will depend on individual body weight.

### 6.3 Cycle 1, Day 8 (C1D8)

Seven days after the first Avelumab infusion (i.e. Cycle 1, Day 8), the subject will initiate HFRT. HFRT must be provided at the study site. Technical details for radiation therapy are provided in **Attachment 6**.

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- Prior to initiating radiation therapy on C1D8, adverse event assessment, a symptom-directed physical exam and limited vital signs (temperature, resting blood pressure, pulse, and respiration rate) must be performed.
- All subjects will receive hypofractionated radiation (HFRT) to a total dose of 25 Gy given as 5 Gy per fraction over 5 consecutive fractions. HFRT must begin 1 week after the first dose of Avelumab (i.e., Day 8 of Cycle 1). HFRT should preferably be given on consecutive days (i.e., Day 8 to Day 12).

#### **6.4 Cycle 1, Day 15 (C1D15) and all subsequent mid-cycle (i.e., Day 15) visits**

The subject will have the C1D15 Safety Procedures detailed below performed prior to initiating study treatment. Required assessments and study drug (Avelumab) administration windows include  $\pm 3$  days of scheduled visit.

- Adverse event assessment
- Symptom-directed physical exam as clinically indicated by the investigator or qualified designee at all mid-cycle visits (i.e. Day 15)
- Vital signs: When scheduled at the same visit as other procedures, vital signs should be measured prior to clinical laboratory assessments or research blood sample collection.
  - Weight (can be taken within 3 days of scheduled Avelumab administration)
  - Vital signs on treatment days subsequent to C1D1 will be assessed and documented prior to the infusion and then approximately 30 minutes after the completion of the infusion (all infusion VS timepoints  $\pm 10$  minutes):
    - Temperature, resting blood pressure, pulse and respiration rate.
    - Note: following all Avelumab infusions, subjects must be observed for 30 minutes post-infusion for potential infusion-related reactions.
- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH)
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
- Urinalysis: glucose, blood, pH, specific gravity, ketones, and urine protein

Avelumab will be administered in an outpatient setting as an IV infusion (see **Treatment Regimen, Section 5.2**). Each patient's dose will depend on individual body weight. The dose of Avelumab must be adjusted each cycle for changes in body weight of  $\geq 10\%$ . Dose adjustments for changes in body weight of  $< 10\%$  will be at the discretion of the investigator.

#### **6.5 Cycle 2, Day 1 (C2D1) and all subsequent Day 1 cycle visits (i.e., C3D1, C4D1)**

The subject will have the C2D1 Safety Procedures detailed below performed prior to initiating study treatment. Required assessments and study drug (Avelumab) administration windows include  $\pm 3$  days of scheduled visit.

- Adverse event assessment
- Complete physical exam, including neurological exam, and KPS assessment

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- Vital signs: When scheduled at the same visit as other procedures, vital signs should be measured prior to clinical laboratory assessments or research blood sample collection.
  - Weight (can be taken within 3 days of scheduled Avelumab administration)
  - Vital signs on treatment days subsequent to C1D1 will be assessed and documented prior to the infusion and then approximately 30 minutes after the completion of the infusion (all infusion VS timepoints  $\pm 10$  minutes):
    - Temperature, resting blood pressure, pulse and respiration rate.
    - Note: following all Avelumab infusions, subjects must be observed for 30 minutes post-infusion for potential infusion-related reactions.
- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH)
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
- Urinalysis: glucose, blood, pH, specific gravity, ketones, and urine protein
- Pregnancy test (urine or serum  $\beta$ -HCG) for women of child-bearing potential
- Research Blood Samples (C2D1 only, not required at subsequent visits): Note: Research blood samples will be taken at only 2 timepoints: **C1D1 (pre-dose)** and **C2D1**. All subjects will have the below research blood samples collected. For details on specimen collection, processing, handling and shipping, refer to **Section 6.8, Attachment 7** and the study **Lab Manual**.
  - NYULMC subjects: 40 mL (four 10 mL purple top EDTA tubes) of whole blood will be drawn and immediately sent to the below sites:
    - One (1) 10 mL tube will be sent to the CBRD at NYULMC for acquisition of whole blood, buffy coat, and plasma samples.
    - Three (3) 10 mL tubes will be sent to the IMC at NYULMC and immediately processed for isolation of PBMCs.
  - Subjects at other sites: 40 mL of whole blood will be collected in two types of tubes provided by NYULMC. All tubes will be shipped overnight to the CBRD at NYULMC per instructions in the **Lab Manual**.
    - 10 mL will be drawn into one Streck Cell-Free DNA BCT® collection tube
    - 30 mL total will be drawn into three 10 mL purple top EDTA tubes and immediately sent to NYULMC.

Avelumab will be administered in an outpatient setting as an IV infusion (see **Treatment Regimen, Section 5.2**). Each patient's dose will depend on individual body weight. The dose of Avelumab must be adjusted each cycle for changes in body weight of  $\geq 10\%$ . Dose adjustments for changes in body weight of  $< 10\%$  will be at the discretion of the investigator.

### **6.6 Cycle 3, Day 1 (C3D1) and then every 8 weeks thereafter**

At C3D1, all required procedures listed in the visit for **Cycle 2, Day 1+** (Section 6.5) will be required except research blood samples. In addition:

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- **Efficacy assessment** consisting of a contrast-enhanced brain MRI or CT will be performed prior to C3D1. Efficacy assessments will then be performed every 8 weeks thereafter. MRIs or CTs can be performed within 7 days (-7 days) of scheduled visit. On-study imaging should follow calendar days (every 8 weeks) and should not be adjusted for delays in cycle starts.
  - Local reading (investigator assessment) will be used to determine eligibility and for participant management. Response Assessments will be performed on every brain imaging assessment performed on protocol per iRANO criteria (see **Section 6.7, Efficacy Procedures**, and **iRANO criteria in Attachment 3**).
- Thyroid stimulating hormone (TSH), free T4

## 6.7 End of Treatment Procedures

Avelumab administration will continue for 2 years or until progression of disease, unacceptable adverse event(s), subject withdrawal of consent, or other event that meets criteria for subject withdrawal or treatment discontinuation as per guidelines outlined in **Section 4.5** and **Section 5.2.3**.

End of treatment assessments below will be performed within 7 days after last drug administration or within 7 days after decision to end treatment.

- Adverse event assessment
- Complete physical exam, including neurological exam, and KPS assessment
- Vital signs: weight, temperature, resting blood pressure, pulse and respiration rate.
- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH)
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
- Urinalysis: glucose, blood, pH, specific gravity, ketones, and urine protein
- Thyroid stimulating hormone (TSH), free T4
- Pregnancy test (urine or serum  $\beta$ -HCG) for women of child-bearing potential

## 6.8 Post Treatment Procedures

**Follow up post-treatment:** All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last study drug. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring and 90 days for serious adverse event reporting. Assessments may continue for ongoing reportable adverse events. Participants removed from protocol therapy for unacceptable adverse events will be following until resolution or stabilization of the adverse event.

**30-day post-drug visit:** A site visit is to be performed at 30 days ( $\pm 7$  days) after the last study drug is given, unless the subject is unable to travel due to deteriorating medical condition, due to the potential risk for delayed immune-related toxicities. The visit will include the safety procedures detailed below:

- Adverse event assessment.
- Symptom-directed physical exam and KPS assessment.
- Vital signs: weight, temperature, resting blood pressure, pulse and respiration rate.

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- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH).
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count.

**90-day post-drug safety follow-up:** An extended safety follow-up is to be performed at 90 days ( $\pm 14$  days) after the last study drug is given. This may be performed via documented phone conversation with a study nurse or clinician or physician.

**Extended follow-up post-treatment:** Subjects should be contacted every 3 months ( $\pm 14$  days) for survival status and initiation of any new anti-cancer treatments until death, withdrawal of permission to record at least survival data, or subject is lost to follow-up. Contact may include clinic visit, telephone contact, e-mail, mail or medical record review. The date of death, initiation of any new anti-cancer treatments and date of last contact should be documented.

If a subject withdraws permission to record at least survival data after coming off treatment, this must be documented along with the date the subject withdraws permission. Subjects will be considered lost to follow up if no medical records are available to be reviewed and two phone calls each to the subject and then the subject's next-of-kin (if the subject does not respond) are not returned over two consecutive 3 month periods.

## 6.9 Efficacy Procedures

Tumor response will be assessed every 8 weeks (see **Section 6.6**) using **iRANO criteria**<sup>70</sup> as outlined. Clinicians may repeat response assessment more frequently as clinically indicated.

Refer to **Attachment 3** for details on iRANO criteria, guidelines for assessing radiologic findings, and treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy.

**Evaluable for objective response.** Only those participants who have measurable disease present at baseline (obtained within 14 days of cycle 1, day 1) scan and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated in **Attachment 3**. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

**Note on continuation of therapy pending confirmation of radiographic disease progression: iRANO** recommends confirmation of disease progression on **follow-up imaging 3 months after initial radiographic progression** if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy (see **Attachment 3** for **iRANO** criteria details). A decision of whether a patient should continue immunotherapy pending confirmation of radiographic disease progression should be established based on perceived benefits and risks. Continuation of immunotherapy may be considered pending follow-up imaging as long as subjects are deriving apparent clinical benefit with minimal and acceptable toxic effects.

By contrast, investigators may consider interrupting immunotherapy for subjects who need a substantial increase in corticosteroids (i.e.,  $>4$  mg of dexamethasone or equivalent per day) for evolving symptoms associated with brain edema or who have more than mild treatment-related toxic effects such as at least grade 2 irAEs. These guidelines are included to limit the likelihood of progressive immunotherapy-induced inflammatory changes leading to substantial deficits in otherwise stable or symptom-free patients. In such subjects, an interruption of immunotherapy dosing might be considered pending follow-up imaging.

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Furthermore, investigators may discontinue or interrupt immunotherapy at any time if this option seems to be in the best medical interest of the subjects. As a general guidance, resumption of immunotherapy might be taken into account when systemic dexamethasone is decreased to 4 mg/day or less and the contrast-enhancing tumor burden is classified as stable disease, partial response, or complete response on a follow-up scan, or when relevant treatment-related toxic effects have resolved to grade 1 or less or pre-treatment baseline.

## 6.10 Research Specimen Procedures

See **Attachment 7** for Background and Rationale of Research Correlative Studies. Refer to the study procedures above in **Section 6.1** and **Section 6.5** for research blood sample collection. Also, refer to the study **Lab Manual** for specific processing and handling procedures for research blood specimens.

Note: This study involves collection of required archival tumor tissue and blood specimens for research as well as collection of an *optional* tumor specimen if a biopsy is required during or after protocol therapy. All patients will be given the option to have leftover research specimens after study completion and completion of protocol-defined research studies banked for future research at the time of informed consent. See **Section 9.1.1** for details on leftover research samples.

### 6.10.1 Archival Tumor Specimen

Archival tumor tissue from a previous surgical resection that demonstrates histopathological evidence of transformation to glioblastoma (GBM, WHO grade IV) or genetic alteration as specified in the **Eligibility Criteria (Section 4.1)** must be submitted.

A paraffin-embedded or frozen tumor-tissue block with a minimum of 1 cm<sup>2</sup> surface area of viable tumor is required. The tumor block should contain at least 20% viable tumor, i.e., a representative H&E slide should show that at least 20% of the specimen contains viable tumor.

If a tumor block cannot be submitted, then twenty (20) unstained 5-micron slides (preferably 10 slides from two different tumor blocks from the same surgery) from the tumor specimen must be submitted.

Note, an archival tumor specimen from the prior lower-grade glioma tumor is not required.

Send archival tumor specimens for research to:

Matija Snuderl, MD  
Department of Pathology, NYU Langone Medical Center  
560 First Avenue  
Tisch Hospital HW 451  
New York, NY 10016  
Phone: 646-501-5281  
Fax: 212-263-7916  
Pager: 917-205-5543  
Matija.Snuderl@nyumc.org

### 6.10.2 Research Blood Samples

Research blood samples will be taken at only 2 timepoints: **C1D1** (up to 3 days prior to C1D1) and at the **C2D1 visit**.

Refer to the **Lab Manual** for specific processing and handling procedures for research blood specimens. All subjects will have the below research blood samples collected. For details on specimen collection, processing, handling and shipping, refer to **Section 6.8** (Study Procedures), **Attachment 7** (Background and Rationale) and the study **Lab Manual**.

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Whole blood for research will be collected from all subjects as described below:

- NYULMC subjects: 40 mL (four 10 mL purple top EDTA tubes) of whole blood will be drawn and immediately sent to the below sites:
  - One (1) 10 mL tube will be sent to the CBRD at NYULMC for acquisition of whole blood, buffy coat, and plasma samples.
  - Three (3) 10 mL tubes will be sent to the IMC at NYULMC and immediately processed for isolation of PBMCs.
- Subjects at other sites: 40 mL of whole blood will be collected in two types of tubes provided by NYULMC. All tubes will be shipped overnight to the CBRD at NYULMC per instructions in the **Lab Manual**. **\*Subsites should NOT schedule research blood draws on Fridays as the NYU CBRD will not be able to receive specimens on weekends.**
- 10 mL will be drawn into one Streck Cell-Free DNA BCT® collection tube
- Three (3) 10 mL purple top EDTA tubes of whole blood will be drawn and immediately shipped to NYULMC and then immediately processed for isolation of PBMCs.

### 6.10.3 Optional Tumor Biopsy for Research

If subjects undergo tumor resections or biopsies during the study period after treatment initiation, or after progression on HFRT + Avelumab, a tumor specimen will be collected for research purposes. For details see **Attachment 7**. A section of frozen tumor or a FFPE block (surface area of 1 cm<sup>2</sup> containing at least 20% viable tumor, as described above in Section 6.8.2) from the tumor surgery is preferred. If a frozen tumor specimen or a tumor block cannot be provided, then 20 unstained 5-micron slides (preferably 10 slides from two different tumor blocks from the same surgery) from the tumor block should be sent.

Send optional tumor samples to:

Matija Snuderl, MD  
Department of Pathology, NYU Langone Medical Center  
560 First Avenue  
Tisch Hospital HW 451  
New York, NY 10016  
Phone: 646-501-5281  
Fax: 212-263-7916  
Pager: 917-205-5543  
Matija.Snuderl@nyumc.org

## 7 Statistical Plan

### 7.1 Sample Size Determination

#### 7.1.1 Background for Statistical Plan:

Secondary GBM outcomes: Although patients with *IDH* mutant gliomas survive relatively longer than those with *IDH* wildtype gliomas from the time of initial diagnosis, nearly all *IDH* mutant gliomas eventually become lethal, with most transforming to "secondary GBM". Outcomes for patients with secondary GBM (transformed *IDH* mutant gliomas), including PFS and OS, have been shown to be equivalent to patients with recurrent "*de novo* GBM", the vast majority of which are *IDH* wildtype.<sup>7,8</sup> The median OS from the time of recurrence or transformation is equivalently

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dismal, ranging from 7-9 months. Therefore, efficacy endpoints for *IDH* wildtype GBM therapeutic clinical trials can be considered equivalent for the *IDH* mutant secondary GBM population.

**PFS6 reference measures:** Previous meta-analyses have demonstrated that PFS6 is an adequate indicator of antitumor benefit for salvage GBM clinical trials and is the standard benchmark used in GBM chemotherapy trials.<sup>71,73,74</sup> Published reference outcomes in recurrent GBM report a PFS6 of 9-15%.<sup>71,73,74</sup> Temozolomide, the only chemotherapy that has demonstrated improved survival in any prospective, randomized phase III trial in GBM,<sup>75</sup> produced a PFS6 of 21% when tested in recurrent GBM patients.<sup>76</sup> More recently, a number of recently reported randomized, prospective trials in recurrent GBM used conventional cytotoxic chemotherapies such as lomustine and carboplatin for the control arm and have reported remarkably similar estimated PFS6 rates in the chemotherapy control arms, ranging between 15%-25%.<sup>77-81</sup> Otherwise, bevacizumab, which was granted accelerated approval by the US FDA for use as monotherapy in progressive GBM in 2009 based on two historically-controlled, single-arm or non-comparative phase II trials,<sup>82,83</sup> has been reported to have relatively higher estimated PFS6 rates of 29% and 42.6%. However, despite improved PFS6 rates observed in phase II trials, the addition of bevacizumab to lomustine failed to show a benefit in overall or neurologic progression-free survival compared to lomustine alone in a multi-institutional, randomized phase III trial of recurrent GBM.<sup>77</sup> Therefore, based on the aggregate results of the above studies, the reference benchmark for our study will be PFS6 of 40%.

**Overall Survival (OS) reference measures:** In recent randomized, controlled trials of recurrent GBM, all of which have failed to demonstrate differences between arms, the median OS of experimental and control arms from the time of recurrence across all of these studies have been remarkably similar and have ranged between 6-10 months, with most arms in these studies reporting a median OS of approximately 9 months.<sup>77-81</sup> These data indicate the chemotherapies in these studies have similar minimal efficacy in recurrent GBM.

With regards to salvage radiotherapy in recurrent GBM, a wide range of outcomes have been reported from numerous retrospective and phase II trials, likely due to small sample sizes, significant selection bias and differences in dose prescriptions and schedules. Notably, however, reported OS rates from the time of salvage re-irradiation are highly similar to recent randomized trials using salvage chemotherapy, with one analysis of >300 recurrent GBM patients reporting PFS6 rates between 28% to 39% and a median 1-year overall survival rate of 26%.<sup>61,66,84-87</sup> Median OS rates reported in re-irradiation studies with larger numbers of patients are also similar to salvage chemotherapy studies, ranging between 7-11 months.<sup>66,84-87</sup> Based on these and other studies, the RTOG 1205 randomized trial of re-irradiation with bevacizumab versus bevacizumab alone uses 9 month OS as the ineffective measure. Based on the aggregate data above, we chose as a reference measure a 1-year median OS rate of 25%.

### 7.1.2 Safety Lead-In sample size determination

Based on the design of the Safety Lead-In and Dose De-Escalation Rules (Refer to Section 5.2.1 and Section 5.2.1.1), the minimum number of patients in the Safety Lead-In will be 6 subjects if the initial dose level (Dose Level 0) is found to be safe and considered the RP2D (**Section 7.1.3**).

If the Safety Lead-In enters into the Dose De-Escalation phase (**Section 5.2.1.1**), then the minimum number of total subjects in the entire study will be 12 if a RP2D cannot be determined. The maximum number of subjects in the Safety Lead-In based on the dose de-escalation design will be 18, with 6 subjects at each Dose Level (**Section 5.2.1.1, Table 1**). If a RP2D is determined after 18 subjects, a total maximal sample size in the entire study of 61 subjects including both the Safety Lead-In and Phase II portions of the study.

### 7.1.3 Phase II trial sample size determination

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Forty-three patients (43) patients will be enrolled and treated in the phase II portion of this trial. All patients who receive one or more doses will be included in the estimate of PFS6. Patients who do not remain on treatment through the 6 cycles will be considered as failures in the primary analysis. With an optimum 2 stage Simon Phase II design, we can test the null hypothesis that  $PFS6 \leq 0.40$  versus the alternative that  $PFS6 \geq 0.60$  with  $\alpha = 0.05$  (actual  $\alpha = 0.047$ ) and power of 80% (actual is 82.7%) with a total of 43 patients. If there are 7 or fewer progression free survivors at 6 months among 18 patients, the study will conclude at the end of stage 1; if there are 8 or more patients surviving for 6 months, the trial will continue for up to 43 patients. If there are 23 or more patients alive without progression by 6 months in the total of 43 patients, the therapy will be considered interesting for further study. Calculations from PASS, NCSS 2014 J. Hintze, Kaysville, UT.

## 7.2 Statistical Methods

### 7.2.1 Safety Lead-In

The Safety Lead-In portion of the study is based on a 3 + 3 design with 3 to 6 patients assigned per dose level. The exact number of patients enrolled in the study will depend on the number of protocol-defined DLTs observed and the need to expand currently defined dose levels, or open additional cohorts at lower dose levels as described in **Section 5.2.1 (Safety Lead-In Design)** and **Section 7.1.2 (Sample Size Determination)**.

The subjects treated at the RP2D in the Safety Lead-In will be included as a separate cohort for the evaluation of outcomes in the phase II study. Data for the Safety Lead-In will be summarized using descriptive statistics. In general, data will be summarized by dose levels. See below in **Section 7.3.1** for Safety Lead-In population for Analysis.

### 7.2.2 Phase II trial

See **Section 7.1.3** for sample size determination. Six months will be defined as six 28-day cycles. Patients will be evaluated for radiographic responses by conventional contrast enhanced MRI every 8 weeks. Radiographic response assessments will be determined using recently developed iRANO criteria for GBM. All subjects who initiate therapy (receive at least one dose of Avelumab and/or radiotherapy) will be evaluated for radiographic response and safety. PFS6 and radiographic response rates will be estimated with exact 95% confidence intervals.

PFS, defined as the time between treatment initiation and first occurrence of disease progression or death, will be censored at last follow-up if the patient remained alive without disease progression. OS will be determined from the time of treatment initiation until the time of death, with OS being censored at last follow-up if the patient remained alive. The Kaplan–Meier curves will be used to summarize PFS and OS and to estimate the medians and 6-month OS and PFS (PFS6).

For toxicity monitoring statistical methods, see the **Primary Safety Endpoints** in **Section 3.4**.

## 7.3 Subject Population(s) for Analysis

### 7.3.1 Safety Lead-In Population

Subjects are evaluable for DLTs if: 1) they experience a DLT at any time during the DLT evaluation period; or 2) in the absence of DLT have received at least one dose of Avelumab and at completed HFRT per protocol and have completed respective safety assessments without major violations over the entire DLT evaluation period. Patients who are not fully evaluable for DLTs during the DLT evaluation period of 28 days following Day 1 will be replaced.

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### 7.3.2 Phase II Trial Efficacy Analysis Population

All subjects that receive at least 1 dose of Avelumab will be included in the primary analysis for the phase II study. The subjects treated at the RP2D in the Safety Lead-In will be included as a separate cohort for the evaluation of outcomes in the phase II study.

### 7.3.3 Safety Analysis Populations

All subjects who received at least one dose of Avelumab will be used for the analysis of safety data in this study. Safety summaries will be reported for both the Safety Lead-In and the phase II trial.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in **Section 3.4** (Primary Safety Endpoints).

## 8 Safety and Adverse Events

### 8.1 Definitions

#### Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

#### Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events.

Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

#### Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs in-patient hospital stay (In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician. Hospitalization or prolongation of existing hospitalization due to the progression of underlying malignancy will not be considered an SAE, if it is clearly consistent with the typical progression pattern of the underlying cancer.

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- results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly or birth defect
- an important medical event - Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

An AE also includes any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

### **Expected Adverse Events for Avelumab**

For the purpose of regulatory reporting requirements during clinical development, the following AEs will be considered as **expected** and meet the threshold of causal association (based on comprehensive medical evaluation considering the mechanism of action and temporal relationship after excluding other possible etiologies) defined by EMD Serono based on safety data from completed and ongoing clinical studies:

- Infusion-related reactions including drug hypersensitivity reactions
- Immune-mediated adverse reactions like immune-mediated colitis, immune-mediated hepatitis including autoimmune hepatitis, immune-mediated thyroid disorders including hyperthyroidism, hypothyroidism, thyroiditis and autoimmune thyroiditis, immune-mediated pneumonitis, immune-mediated skin reactions including rash, pruritus, rash generalized, rash maculo-papular, erythema, pemphigoid, other immune-mediated reactions including myocarditis, adrenal insufficiency, uveitis, iritis, myositis.

Note: Development of edema in the brain is common following fractionated brain radiation therapy and may be asymptomatic (solely a radiographic finding) or associated with mild, moderate or severe symptoms. Therefore, brain edema will be considered an expected event related to study therapy (HFRT).

### **Progression of underlying malignancy**

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered a SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in **Section 8.4**.

### **Adverse Event Reporting Period**

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

### **Preexisting Condition**

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

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### **General Physical Examination Findings**

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

### **Post-study Adverse Event**

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

### **Abnormal Laboratory Values**

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. more frequent follow-up assessments, further diagnostic investigation, etc.
- The abnormality leads to a change in dosing (outside of protocol-stipulated dose adjustments)
- The abnormality leads to discontinuation from the study, significant additional concomitant medication, or other therapy

Contact the sponsor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in **Section 8.2.1**.

### **Hospitalization, Prolonged Hospitalization or Surgery**

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

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## 8.2 Evaluation of Severity and Causality

### 8.2.1 Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system. Adverse events not listed in the NCI-CTCAE, will be graded according to the following scale:

- |                              |  |
|------------------------------|--|
| <b>1 (Mild):</b>             | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.   |
| <b>2 (Moderate):</b>         | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.  |
| <b>3 (Severe):</b>           | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| <b>4 (Life-threatening):</b> | Life-threatening consequences; urgent intervention indicated.  |
| <b>5 (Death):</b>            | Death related to AE.   |

\* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

\*\*Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### 8.2.2 Evaluation of Causality

#### Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

**Not Related:** There is no reasonable possibility that the event may have been caused by the study drug

**Related:** There is a reasonable possibility that the event may have been caused by the study drug.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

**Attachment 5** lists factors to consider in assessing the relationship of AEs to Avelumab or infusion procedures, radiation therapy, combination treatment, study procedures, or background treatment.

## 8.3 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

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All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

#### **8.4 Reporting of Serious Adverse Events and Unanticipated Problems**

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 30 days after the end of study treatment. CTCAE version 4.03 terms should be used.

All AEs after initiation of study treatment and until 30 days after the last study treatment, regardless of relationship to study treatment, will be reported. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 30 days after last study treatment should be reported. Information for any nonserious AE that starts during the treatment period or within 30 days after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first. Serious adverse event information will be collected until the event is considered chronic and/or stable.

Study treatment includes Avelumab and radiation therapy.

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

Serious adverse event reporting will begin in conjunction with the date of informed consent. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the Sponsor or its designee and recorded on the case report form.

All fatal or life-threatening adverse events must be immediately reported to the Sponsor by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event (SAE) Form supplied by NYULMC must be faxed to the Sponsor, who must then inform the NYULMC IRB, PCC CTO, and DSMC within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of study drug (Avelumab), even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor immediately (within 1 working day) using the AE and SAE forms supplied by NYULMC. Overdose of study drug will be defined as at least 2 times the intended dose of study drug within the intended therapeutic window.

All serious adverse events (SAEs) will be evaluated by the DSMC. If meeting the requirements for expedited reporting, the Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The investigator is responsible for reporting all SAEs to the appropriate IRB, DSMC, and FDA.

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### For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

#### 8.4.1 Investigator reporting: notifying the study sponsor, NYULMC IRB, Perlmutter Cancer Center Clinical Trials Office, and EMD Serono/Merck KGaA

The following describes events that must be reported to the study sponsor in an expedited fashion.

##### Initial Report: within 24 hours of awareness of the event:

The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.
- Symptomatic Overdose of Study Drug, Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.
- Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), by telephone within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 90 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE. All pregnancy outcomes will be followed.
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.
- Adverse Events of Special Interest (AESI)

An AE of special interest (AESI) may or may not be a DLT or SAE. AESIs must be reported within 24 hours of awareness of the event to the **Sponsor/Overall PI** and the local institution's DSMC and IRB per institutional guidelines. If the AESI is **not** an SAE or DLT, there is no need to report within 24 hours to the local institution's DSMC or IRB unless specified specifically by the local institution's guidelines. AEs of special interest for this study include:

- Any AE that meets DLT criteria (see **Section 5.2.1.2**)
- Grade 2 or greater infusion-related reactions (See **Section 5.2.3.5**)
- Grade 2 or greater allergic/hypersensitivity reactions (see **Section 5.2.3.5**)
- Grade 3 or greater symptoms suspected to be attributable to brain edema (see **Section 5.2.1.2 for Rules for Brain Edema**).
- Grade 3 or greater immune-related toxicities (irAE) (see **Section 5.2.3.3**)

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In the event the investigator is informed of an SAE that occurs after 30 days after the last dose of study treatment, only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered chronic and/or stable.

Additionally, an FDA Form 3500A (MEDWATCH Form) must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site or can be obtained from the FDA website:

<http://www.fda.gov/safety/medwatch/howtoreport/downloadforms/default.htm>.

**Contact information for submission of reportable events to the Sponsor (NYULMC):**

NYUPCCsafetyreports@nyumc.org

AND

Sylvia Kurz, MD, PhD  
Laura and Isaac Perlmutter Cancer Center  
NYU Langone Medical Center  
240 East 38th Street, 19th Floor  
New York, NY 10016  
Phone: 212-731-6267  
Fax: 646-754-9696  
Email: Sylvia.Kurz@nyulangone.org

**Follow-up report: within 48 hours of awareness of the event:**

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event.

Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

**New information available after 48 hours of initial event: within 24 hours of awareness of new information**

If new information about a previously reported event becomes available 48 hours after the initial awareness of the event, this new information should be reported within 24 hours of awareness of the new information. Any new follow-up information that is received or that the investigator is newly made aware of after the initial 48 hour reporting period should be reported within 24 hours from the time of awareness of the new information.

**Other Reportable events:**

- **Deviations from the study protocol**  
Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but **no later than 5 working days** of the protocol deviation.
- **Withdrawal of IRB approval**  
An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but **no later than 5 working days** of the IRB notification of withdrawal of approval.

**8.4.2 Investigator reporting: notifying the IRB**

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Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protection (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting-Improving Human Subject Protection." The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record. The NYU IRB address is:

NYULMC IRB  
1 Park Avenue, 6<sup>th</sup> Floor  
New York, NY 10016

**Report Promptly, but no later than 5 working days:**

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events that are unexpected and related***
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

**Other Reportable events:**

The following events also require prompt reporting to the IRB, though **no later than 5 working days**:

- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- **Breach of confidentiality**
- **Incarceration of a participant** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

**Reporting Process**

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

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### 8.4.3 Sponsor reporting: *Notifying the FDA*

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days (via telephone or facsimile report)***  
Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening
  
- ***Within 15 calendar days (via written report)***  
Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

-or-

  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).
  
- Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

#### **Additional reporting requirements**

Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

#### **Reporting Process**

Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form, obtained from the FDA website: <http://www.fda.gov/safety/medwatch/howtoreport/downloadforms/default.htm>), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

Email: [NYUPCCsafety@nyumc.org](mailto:NYUPCCsafety@nyumc.org)  
Tel: 212-263-4427

### 8.4.4 Sponsor Reporting: *Notifying EMD Serono*

The following reportable events must be submitted to the Sponsor (NYULMC) within 24 hours (or immediately for death or life-threatening events) using the applicable safety report form provided. The Sponsor/Overall PI will assume responsibility for submitting the reportable event(s) to EMD Serono within 2 business days or 3 calendar days (whichever comes first), as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Contact information for submission of reportable events to Sponsor/Overall Principal Investigator:

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NYUPCCsafetyreports@nyumc.org

AND

Sylvia Kurz, MD, PhD  
Laura and Isaac Perlmutter Cancer Center  
NYU Langone Medical Center  
240 East 38th Street, 19th Floor  
New York, NY 10016  
Phone: 212-731-6267  
Fax: 646-754-9696  
Email: Sylvia.Kurz@nyulangone.org

Specifying:

- PROTOCOL Number and/or Title
- EMD Serono assigned Study Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

#### 8.4.5 Sponsor reporting: Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as note above in **Section 8.4.3**. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

### 8.5 Stopping Rules

For the **Safety Lead-In**, see **Section 5.2.1, Safety Lead-In Treatment Regimen**, for detailed rules for continuing enrollment, dose decisions, and study discontinuation. In summary, once each cohort has filled enrollment, enrollment will stop and subjects will be observed for 28 days for dose-limiting toxicities (DLTs). At the end of each DLT period, the Safety Monitoring Team will review the safety data at a Safety Lead-In Dose Review meeting that will include at least a representative from each site; sub-investigators may be included. Continuation of enrollment will occur once all of the subjects have completed the Day 28 safety assessments of that particular cohort and the final dosing decisions, including whether the study should be discontinued or proceed to phase II, will be made by the Safety Monitoring Team.

For the Phase II trial, stopping rules for unexpected toxicity are outlined in see **Section 3.4, Primary Safety Endpoints**, and stopping rules for futility at the end of stage 1 of the phase II trial are outlined in **Section 7.2.2, Statistical Methods**.

### 8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see **Section 10 Auditing, Monitoring and Inspecting**). Adverse events are evaluated monthly by the principal investigator in conjunction with the research team. The Data Safety and Monitoring Committee (DSMC) will review the study twice a year. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

#### 8.6.1 Data and Safety Monitoring Committee

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This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the 2011 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYULMC Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULMC PCC. Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase 2 trial will be monitored by DSMC twice annually (from the date the first patient is enrolled), at dose escalation point and subsequent cohort activation, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Accrual to the next dose within a cohort will be held until real-time review of the toxicity from the prior cohort has occurred to assure no defined DLTs have occurred prior to proceeding to the next level or expanding the current cohort. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 6-8 weeks.

Other external sites will be monitored and informed of other adverse events by the medical monitor within 7 days of toxicities and within 3 business days of SAE. Scheduled conference calls will be conducted after 3 patients are enrolled and at each dose escalation point. Additional conference calls will be scheduled as indicated based on the recommendations from the medical monitor, the Overall PI of this study.

## **9 Data Handling and Record Keeping**

### **9.1 Confidentiality**

The study team will maintain clinical and laboratory data in a designed manner to ensure patient confidentiality. All study personnel have passed human subject protection courses. If applicable, tissue samples sent to collaborators outside of NYULMC will only be labeled with an assigned protocol-subject identification number without patient identifiers. Systems used for electronic data capture are compliant with HIPAA and applicable local regulatory agency guidelines. All documents are kept in strictly confidential files and are only made accessible for specific study personnel, CTO quality assurance specialists, and authorized representatives of regulatory agencies as described in the informed consent document.

#### **9.1.1 Leftover Research Samples (Tissue and Blood)**

At the time of informed consent to participate in this trial, patients will have the option to allow all research samples (archival tumor sample, research blood samples, and optional tumor biopsy sample) remaining after completion of the study and protocol-specified correlative biomarker research to be banked for future research studies. Future studies may include, but are not limited to, genetic, epigenetic, and molecular studies with the overall goal of correlating any scientific findings with the patients' outcome to protocol therapy. Leftover samples will be stored in a repository in the NYULMC Center for Biospecimen Research and Development (CBRD) and labeled with an assigned protocol-patient identification number without subject identifiers. The assigned protocol-patient identification numbers will be stored in a central database on a password-protected NYULMC server. This central database will contain the key to decoding assigned protocol-patient identification numbers used for sample labeling and patient's identifiable medical information (PHI). Only the Overall PI will have the linking key to the subject identifiers.

For each leftover research sample, key clinical information including, but not limited to, gender, age at diagnosis, tumor location, prior treatment and histology will be abstracted from the medical record and recorded with the assigned protocol-patient identification number on a separate database from the central

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database containing the identifiable PHI. This de-identified database will also be on a password-protected NYULMC server and will be administered by the overall PI. Only the Overall PI and IRB-approved study investigators with permission from the Overall PI will have access to this de-identified database.

The de-identified samples and data may be made available to researchers at NYULMC (NYU Langone Medical Center), NYU SoM (NYU School of Medicine), and other NYULMC affiliates, as well as researchers outside of NYU. De-identified samples may be shared with for-profit companies that are working with NYULMC, NYU SoM or other NYULMC affiliate researchers on a specific IRB-approved research project. De-identified specimens may also be made available to other researchers through research organizations whose mission focuses on the acquisition, authentication, production, preservation, development and/or distribution of data and materials for research in the life sciences, such as The Cancer Genome Atlas, a collaboration between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI).

Patients not agreeing to allow their leftover samples/data to be stored for future use will be able to fully participate in the study with no restrictions. The central database and de-identified database maintained for at least 5 years after termination of the study.

If a result from a genetic test on mandatory or leftover research samples is deemed by the Study Sponsor/Overall PI to be important to report to the subject, the Subject may elect at the time of informed consent to receive results of genetic tests. If results are shared with the subject, the genetic test result will be validated with a repeat genetic test prior to sharing the information with the subject. The subject must consent to have a consultation with a genetic counselor at the participating institution at the time results are released. The costs associated with the genetic counselor involved with the disclosure of these potentially clinically important results may be billed to the subject's insurance company or other third parties, if appropriate, and the subject may also be responsible for some of them. The funding sponsor (EMD Serono, Inc.) will not pay for costs for the genetic counselor involved with the disclosure of these potentially clinically important results.

Subjects can withdraw their samples/data from future use at any time. The subject may contact the Study Sponsor/Overall PI or designee to express his or her wish to withdraw leftover samples from storage.

## **9.2 Confidentiality and HIPAA**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

## **9.3 Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, microfilm or magnetic media, x-

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rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

#### **9.4 Data and Source Documentation**

Velos, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned research coordinator, and CTO quality assurance specialists will have access to the database. Velos is the primary data collection instrument for the study. All data requested in Velos must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 6-8 weeks for data entry accuracy.

#### **9.5 Records Retention**

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

### **10 Study Monitoring, Auditing, and Inspecting**

#### **10.1 Study Monitoring Plan**

This study will be monitored according to the monitoring plan detailed below. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform EMD Serono/Merck KGaA of any audit requests by health authorities, and will provide EMD Serono/Merck KGaA Pharmaceuticals with the results of any such audits and with copies of any regulatory documents related to such audits.

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In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

- (1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.
- (2) DSMC, twice annually
- (3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.
- (4) In addition, the quality assurance unit will monitor this trial every 6-8 weeks, to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

## **10.2 Auditing and Inspecting**

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

## **11 Ethical Considerations**

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice (GCP), and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal

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consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

## 12 Study Finances

### 12.1 Funding Source

Funding for conducting the trial will be provided by EMD Serono/Merck KGaA. The investigational agent (Avelumab) will be provided to patients enrolled on this study by EMD Serono/Merck KGaA.

### 12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

### 12.3 Subject Stipends or Payments

No patient or subject will receive payments or stipends for participation in this research study. EMD Serono/Merck KGaA may provide coverage for tests and/or procedures that are a part of the research study, if it is not covered by the subject's insurance.

## 13 Publication Plan

NYULMC fulfills its commitment to publicly disclose the results of studies.

The overall Principal Investigator, Sylvia Kurz, M.D., Ph.D., holds the primary responsibility for publication of the study results. The co-investigators of this study must first obtain approval from Dr. Kurz, the primary responsible party for publication, before any information collected in this trial can be used or passed on to a third party. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the overall Principal Investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of the study overall Principal Investigator. Any investigator involved with this study is obligated to provide the overall Principal Investigator with complete test results and all data derived from the study.

EMD Serono/Merck KGaA has no objection to publication by the study overall Principal Investigator of any information collected or generated by the study overall Principal Investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, Investigator will provide EMD Serono/Merck KGaA an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

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## 15 Attachments

**Attachment 1: Schedule of Events**

**Attachment 2: Karnofsky Performance Status Scale**

**Attachment 3: iRANO Criteria**

**Attachment 4: Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific Drug-Related Adverse Events**

**Attachment 5: Factors to Consider in Assessing the Relationship of AEs to Avelumab or Infusion Procedure, Study Procedure, or Combination Treatment**

**Attachment 6: Technical Specifications and Structural Considerations for Planning Radiotherapy**

**Attachment 7: Research Correlative/Biomarker Studies: Background and Rationale**

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## 15.1 Attachment 1: Schedule of Events

STUDY DAY ►	Day -21 to -1 <sup>1</sup>	C1 D1 <sup>4</sup>	C1 D8 <sup>11</sup>	C1 D15 <sup>5</sup>	C2 D1	C2 D15	D1 of C3+	End of Rx <sup>26</sup>	30-Day Post-Drug <sup>27</sup>	90-Day Post-Drug <sup>28</sup>
<b>Study Team Procedures</b>										
Informed Consent <sup>2</sup>	X									
Demographics	X									
Inclusion/Exclusion Criteria <sup>3</sup>	X									
Medical/Disease History <sup>6</sup>	X									
KPS Assessment <sup>8</sup>	X	X			X		X	X	X	
Concomitant Medications <sup>9</sup>	X	X			X		X	X	X	
Height and Weight <sup>10</sup>	X	X		X	X	X	X	X	X	
Vital Signs <sup>11</sup>	X	X	X	X	X	X	X	X	X	
Complete Physical Exam <sup>12</sup>	X	X			X		X	X		
Directed Physical Exam <sup>13</sup>			X	X		X			X	
Adverse Events <sup>25</sup>		X	X		X		X	X	X	X
Survival								X	X	X
<b>Laboratory/Cardiology Assessments</b>										
Serum Chemistry <sup>14</sup>	X	X		X	X	X	X	X	X	
Hematology <sup>15</sup>	X	X		X	X	X	X	X	X	
Urinalysis <sup>16</sup>	X			X	X	X	X	X		
Coagulation <sup>17</sup>	X									
Hepatitis B and C <sup>29</sup>	X									
Pregnancy Test <sup>18</sup>	X	X			X		X	X		
TSH, free T4 <sup>19</sup>	X	X					X (every other cycle)	X <sup>19</sup>		
12-Lead ECG	X									
<b>Study Treatment</b>										
Radiotherapy: 5 Gy x 5 fractions (25 Gy total) <sup>20</sup>			X <sup>11</sup>							
Avelumab IV <sup>21</sup>		X		X	X	X	X			
<b>Imaging Assessments</b>										
MRI Brain Scan <sup>22</sup>	X						X			
Chest X-ray <sup>30</sup>	X									
<b>Research Samples</b>										
Archival tumor tissue <sup>7</sup>	X									
Research blood samples <sup>23</sup>		X			X					
Tumor biopsy (optional) <sup>24</sup>								X		

### EXPLANATION OF SUPERSCRIPTS:

1. Screening will start within 21 days prior to initiation of study treatment (first dose of Avelumab).
2. Informed Consent: Performed by MD attending only. Informed consent process to be fully documented: e.g. prospective participant had sufficient time for deliberation, all questions were answered, treatment options provided by MD, full study reviewed including risks, and a copy of signed consent given to the participant. No study specific screening procedures may occur until after the informed consent process is complete. Informed consent may be obtained more than 21 days before the start of screening procedures. Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.

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3. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all eligibility criteria must be available prior to registration.
4. C1D1 assessments must be performed within 3 days prior to the first dose of Avelumab.
5. If well tolerated and no tumor progression, clinic visits and laboratories will be conducted every 2 weeks with radiographic assessment performed every 8 weeks (approximately every 2 cycles). For all study visits subsequent to C1D8, required assessments must be performed within 3 days of each scheduled Visit Day.
6. All patients must have histopathological documentation of a prior lower-grade (WHO grade II or III) glioma on a previous biopsy specimen and documentation of temozolomide or PCV chemotherapy prior to transformation to glioblastoma (WHO grade IV). All patients must have histopathological diagnosis of glioblastoma, WHO grade IV, at progression from the prior grade II or III glioma. The diagnosis of glioblastoma must be confirmed by central review prior to registration. An *IDH1* or *IDH2* mutation must be present in at least one tumor specimen. Subjects who received anti-tumor therapy after histopathologic transformation to glioblastoma must have shown unequivocal radiographic evidence of tumor progression by contrast-enhanced MRI scan (or CT scan if MRI is contraindicated). Medical history should also include review of all treatment history for GBM and any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
7. After registration, all patients will be required to provide a tumor block with a minimum of 1 cm<sup>2</sup> of tumor surface area from a previous tissue specimen that demonstrates pathological transformation to glioblastoma (WHO grade IV). If a tumor block cannot be submitted, then 20 unstained slides (preferably 10 slides from two different tumor blocks from the same surgery) from the tumor specimen must be submitted.
8. Karnofsky Performance Status (KPS) assessment: See **Attachment 2** for KPS scale.
9. Concomitant medication recording will be ongoing throughout the course of the study. Record concomitant medications from within 21 days before starting study treatment up to the 30-Day Post Drug Visit.
10. Height is required only at screening. Weight can be taken within 3 days of scheduled study drug administration.
11. Vital signs include temperature, resting blood pressure, pulse, and respiration rate. When scheduled at the same visit as other procedures, vital signs should be measured prior to clinical laboratory assessments or research blood sample collection. At C1D1, vital signs will be collected prior to treatment, at the end of the infusion, and 30 minutes post-infusion. Vital signs on subsequent treatment days of cycle 1 and all subsequent cycles will be assessed and documented prior to the infusion and then approximately 30 minutes after the completion of the infusion (all infusion VS timepoints  $\pm$ 10 minutes). Following all Avelumab infusions, subjects must be observed for 30 minutes post-infusion for potential infusion-related reactions. During Radiation Therapy, vital signs will only be recorded on the first day of radiation therapy (C1D8).
12. Complete physical exam to be completed by the investigator or qualified designee at screening, C1D1 and start of all subsequent cycles. Complete physical exam includes skin, head, eyes, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, extremities, and neurological exam. The exam may be performed within 3 days prior to the day of each scheduled study visit.
13. Symptom-directed physical exam to be completed as clinically indicated by the investigator or qualified designee on the first day of radiation therapy (C1D8) and at all mid-cycle visits (i.e. Day 15).
14. Serum Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). Samples may be collected within 3 days prior to the scheduled day of each visit.
15. Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count. Samples may be collected within 3 days prior to each scheduled study visit.
16. Urinalysis: glucose, blood, pH, specific gravity, ketones, and urine protein. Samples may be collected within 3 days prior to each scheduled study visit.
17. Coagulation – PT/INR, PT, PTT required at screening only.
18. Urine or serum  $\beta$ -HCG for women of child-bearing potential at screening and at Day 1 of every cycle.
19. TSH (thyroid stimulating hormone) and free T4 (free thyroxine) at C1D1, every other cycle thereafter, and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).
20. Hypofractionated radiation therapy (HFRT): Administered 5 Gy per fraction for 5 fractions over 5 consecutive days. Total HFRT dose will be 25 Gy. See **Attachment 6** for technical details of HFRT. On the first day (C1D8) of HFRT, adverse event assessment, a symptom-directed physical exam and limited vital signs (temperature, resting blood pressure, pulse, and respiration rate) must be performed.
21. Study drug (Avelumab) administration windows include  $\pm$ 3 days of scheduled visit. Avelumab will be administered in an outpatient setting as an IV infusion. Each patient's dose will depend on individual body

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- weight. The dose of Avelumab must be adjusted each dose for changes in body weight of  $\geq 10\%$ . Dose adjustments for changes in body weight of  $< 10\%$  will be at the discretion of the investigator.
22. Contrast-enhanced brain MRI for response assessment will be performed prior to C1D1, then prior to C3D1, and then every 8 weeks thereafter. Initial imaging should be performed within 14 days prior to first dose of study treatment (Avelumab). MRIs can be performed within 7 days (-7 days) of scheduled assessment. On-study imaging should follow calendar days (every 8 weeks) and should not be adjusted for delays in cycle starts. A contrast-enhanced CT can be performed if MRI is contraindicated. Local reading (investigator assessment) will be used to determine eligibility and for participant management. Response Assessments will be performed on every brain imaging assessment performed on protocol per iRANO criteria (see **Attachment 3**).
  23. Research Blood Samples: For all patients, whole blood will be drawn at two timepoints: C1D1 (pre-dose) and at C2D1. For subjects at NYULMC, four purple top EDTA tubes (40 mL) will be drawn, one EDTA tube will be sent to the CBRD and three EDTA tubes will be sent immediately to the IMC. For subjects at other sites: **\*Subsites should NOT schedule research blood draws on Fridays as the NYU CBRD will not be able to receive specimens on weekends.** 40 mL of blood will be drawn into two types of tubes: 10 mL will be drawn into one Cell-Free DNA BCT® collection tube and 30 mL will be drawn into three purple top EDTA (10 mL) tubes. Blood samples will be immediately shipped overnight to NYULMC per instructions in the **Lab Manual**.
  24. Optional tumor biopsy: If subjects undergo tumor resections or biopsies during the study period after treatment initiation, or after progression on HFRT + Avelumab, a tumor specimen will be collected for research purposes. For details see **Section 6.8.3** and **Attachment 7**.
  25. Monitored throughout the study via safety assessments, observation, and participant reporting.
  26. End of treatment assessments to be performed within 7 days after the last drug administration or within 7 days after decision to end treatment. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring and 90 days for serious adverse event reporting. Assessments may continue for ongoing reportable adverse events. After coming off study, patients will be contacted every 3 months to assess survival status.
  27. A site visit is to be performed at 30 days ( $\pm 7$  days) after the last study drug is given, unless the subject is unable to travel due to deteriorating medical condition, due to the potential risk for delayed immune-related toxicities. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last study drug.
  28. Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days ( $\pm 14$  days) after the last dose of avelumab administration. The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call. This may be performed via documented phone conversation with a study nurse or physician.
  29. Hepatitis B virus surface antibody, hepatitis B virus surface antigen, hepatitis B virus core antibody, and hepatitis C virus antibody at screening only.
  30. Chest x-ray is required at screening if not performed within 60 days prior to initiation of study treatment.

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**15.2 Attachment: 2**

***Karnofsky Performance Status Scale***

<b>Karnofsky Performance Scale</b>	
<b>Percent</b>	<b>Description</b>
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.

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### 15.3 Attachment: 3

## ***iRANO (immunotherapy response assessment in neuro-oncology) Criteria***

Tumor response will be assessed every 8 weeks for patients treated on this study using modified iRANO criteria<sup>70,88</sup> as outlined in the **Study Procedures (Section 6)**.

### **Anti-Tumor Effect Definitions**

Evaluable for objective response. Only those participants who have measurable disease present at baseline (obtained within 14 days of cycle 1, day 1) scan and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

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 which are at least 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-measurable 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.

### **Response/Progression Categories**

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

1. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
2. No new lesions\*.
3. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
4. Participants must be on no steroids or must not be on increased doses of steroids within 2 weeks of assessment relative to the dose taken at the time of the previous assessment
5. Stable or improved non-enhancing (T2/FLAIR) lesions
6. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related

*Participants with non-measurable disease cannot have a complete response. The best response possible is stable disease.*

*\*See immunotherapy considerations below regarding new lesions*

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

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1. Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
2. No progression of non-measurable disease.
3. No new lesions.\*
4. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
5. Participants must be on no steroids or must not be on increased doses of steroids within 2 weeks of assessment relative to the dose taken at the time of the previous assessment
6. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
7. Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

*Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.*

*\*See immunotherapy considerations below regarding new lesions*

Progressive disease (PD). Any of the following criterion must be met:

1. 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
2. Patients who decrease corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment cannot be classified as having progressive disease and should be classified as non-evaluable.
3. Any new enhancing measurable lesion\*
4. 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.
5. Failure to return for evaluation due to death or deteriorating condition

*\*See immunotherapy considerations below regarding new lesions*

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

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

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

#### Special Considerations for Immunotherapies.

Appearance of new lesions is a criterion that defines progression of disease by RANO criteria. However, transient appearance of new enhancing lesions at either local or distant sites might occur in patients with neuro-oncological malignancies receiving immunotherapy. In such situations, careful radiological and clinical assessments are warranted. In some cases, new enhancing lesions might represent immune responses directed against infiltrative brain tumor cells. In addition, Immune-related response criteria guidelines for non-brain tumor cancers state that early increases in lesion size or new lesions do not

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define progressive disease unless further progressive changes are confirmed upon follow-up imaging, provided that patients do not have a clinical decline.<sup>72</sup> Therefore, confirmation to define progressive disease is an important, novel aspect of immune-related response criteria. Additionally, the converse argument, the need of follow-up imaging to confirm a radiographic response, has been an accepted component of most response assessment metrics including RANO.

Confirmation of radiographic progression to define progressive disease in iRANO:

- iRANO recommends confirmation of disease progression on follow-up imaging **3 months after initial radiographic progression** if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy.
- Imaging within the 3-month follow-up can be done as medically appropriate at the discretion of the treating clinician.
- The appearance of new lesions 6 months or less from the initiation of immunotherapy alone does not define progressive disease.
- If follow-up imaging confirms disease progression, the date of actual progression should be back-dated to the date of initial radiographic progression.

Note on continuation of therapy pending confirmation of radiographic disease progression: **iRANO** recommends confirmation of disease progression on **follow-up imaging 3 months after initial radiographic progression** if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy (see **Attachment 3** for **iRANO** criteria details). A decision of whether a patient should continue immunotherapy pending confirmation of radiographic disease progression should be established based on perceived benefits and risks. Continuation of immunotherapy may be considered pending follow-up imaging as long as subjects are deriving apparent clinical benefit with minimal and acceptable toxic effects.

By contrast, investigators may consider interrupting immunotherapy for subjects who need a substantial increase in corticosteroids (i.e., >4 mg of dexamethasone or equivalent per day) for evolving symptoms associated with brain edema or who have more than mild treatment-related toxic effects such as at least grade 2 irAEs. These guidelines are included to limit the likelihood of progressive immunotherapy-induced inflammatory changes leading to substantial deficits in otherwise stable or symptom-free patients. In such subjects, an interruption of immunotherapy dosing might be considered pending follow-up imaging.

Furthermore, investigators may discontinue or interrupt immunotherapy at any time if this option seems to be in the best medical interest of the subjects. As a general guidance, resumption of immunotherapy might be taken into account when systemic dexamethasone is decreased to 4 mg/day or less and the contrast-enhancing tumor burden is classified as stable disease, partial response, or complete response on a follow-up scan, or when relevant treatment-related toxic effects have resolved to grade 1 or less or pre-treatment baseline.

The iRANO Response Criteria to be used in this study are summarized in the Table below.

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### Summary of iRANO Response Criteria

Complete response	Disappearance of all enhancing disease for $\geq 4$ weeks; no new lesions; stable or improved T2/FLAIR; no more than physiological steroids; clinically stable or improved
Partial response	$\geq 50\%$ decrease in the sum of biperpendicular diameters of enhancing disease for $\geq 4$ weeks; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved
Minor response	NA
Stable disease	Does not qualify for complete response, partial response, or progressive disease; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved
Progressive disease	$\geq 25\%$ decrease in the sum of biperpendicular diameters of enhancing disease; or new lesions; or substantial worsened T2/FLAIR; or substantial clinical decline

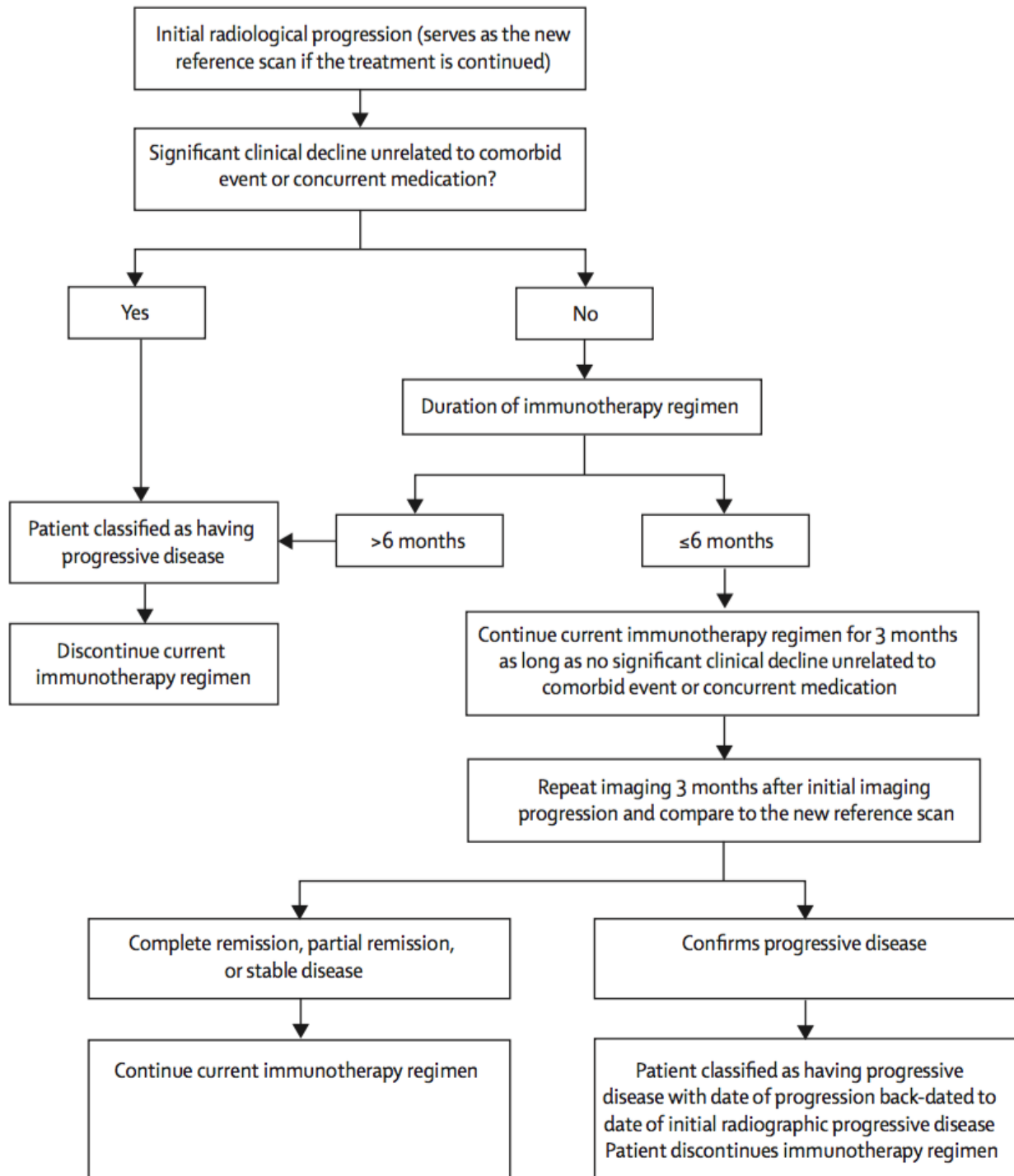
**Note:** iRANO recommends confirmation of disease progression on follow-up imaging 3 months after initial radiographic progression if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy. If follow-up imaging confirms disease progression, the date of actual progression should be back-dated to the date of initial radiographic progression. The appearance of new lesions 6 months or less from the initiation of immunotherapy alone does not define progressive disease. FLAIR=fluid-attenuated inversion recovery.

**Note:** Typographical error in the Progressive Disease definition, the correct criteria should be "increase" rather than "decrease".

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### iRANO treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy



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**15.4 Attachment: 4**

***Dose Modification or Discontinuation and Supportive Care Guidelines  
for Specific Drug-Related Adverse Events***

<b>Gastrointestinal irAEs</b>		
<b>Severity of Diarrhea/Colitis (NCI-CTCAE v4)</b>	<b>Initial Management</b>	<b>Follow-up Management</b>
<p><b>Grade 1</b> Diarrhea: &lt; 4 stools/day over Baseline Colitis: asymptomatic</p>	<p>Continue avelumab therapy Symptomatic treatment (e.g. loperamide)</p>	<p>Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.</p>
<p><b>Grade 2</b> Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated &lt; 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool</p>	<p>Withhold avelumab therapy Symptomatic treatment</p>	<p>If improves to Grade ≤ 1: Resume avelumab therapy  If persists &gt; 5-7 days or recurs: Treat as Grade 3 or 4.</p>
<p><b>Grade 3 to 4</b> Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation</p>	<p>Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3.  1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy</p>	<p>If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).  If worsens, persists &gt; 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.</p>

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<b>Dermatological irAEs</b>		
<b>Grade of Rash (NCI-CTCAE v4)</b>	<b>Initial Management</b>	<b>Follow-up Management</b>
<b>Grade 1 to 2</b> Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy  Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
<b>Grade 3 to 4</b> Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
<b>Pulmonary irAEs</b>		
<b>Grade of Pneumonitis (NCI-CTCAE v4)</b>	<b>Initial Management</b>	<b>Follow-up Management</b>
<b>Grade 1</b> Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
<b>Grade 2</b> Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.

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	<p>prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy</p>	
<p><b>Grade 3 to 4</b> Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening</p>	<p>Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy</p>	<p>If improves to Grade <math>\leq</math> 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)</p>
<b>Hepatic irAEs</b>		
<b>Grade of Liver Test Elevation (NCI-CTCAE v4)</b>	<b>Initial Management</b>	<b>Follow-up Management</b>
<p><b>Grade 1</b> Grade 1 AST or ALT <math>&gt;</math> ULN to 3.0 x ULN and/or Total bilirubin <math>&gt;</math> ULN to 1.5 x ULN</p>	<p>Continue avelumab therapy</p>	<p>Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.</p>
<p><b>Grade 2</b> AST or ALT <math>&gt;</math> 3.0 to <math>\leq</math> 5 x ULN and/or total bilirubin <math>&gt;</math> 1.5 to <math>\leq</math> 3 x ULN</p>	<p>Withhold avelumab therapy Increase frequency of monitoring to every 3 days.</p>	<p>If returns to Grade <math>\leq</math> 1: Resume routine monitoring; resume avelumab therapy. If elevation persists <math>&gt;</math> 5 to 7 days or worsens: Treat as Grade 3 to 4.</p>
<p><b>Grade 3 to 4</b> AST or ALT <math>&gt;</math> 5 x ULN and/or total bilirubin <math>&gt;</math> 3 x ULN</p>	<p>Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically</p>	<p>If returns to Grade <math>\leq</math> 1: Taper steroids over at least 1 month If does not improve in <math>&gt;</math> 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.</p>

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	warranted	
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	Initial Management	Follow-up Management
<b>Grade 1</b> Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
<b>Grade 2 to 3</b> Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
<b>Grade 4</b> Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	Initial Management	Follow-up Management
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.*  Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy.  If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.

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Immune-mediated myocarditis	<p>Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.</p>	<p>Once improving, taper steroids over at least 1 month.</p> <p>If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).</p>
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\*Local guidelines, or eg. ESC or AHA guidelines  
 ESC guidelines website: <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines>  
 AHA guidelines website:  
<http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001>

<b>Endocrine irAEs</b>		
<b>Endocrine Disorder</b>	<b>Initial Management</b>	<b>Follow-up Management</b>
<p><b>Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)</b></p>	<p>Continue avelumab therapy Endocrinology consult if needed</p> <p>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate.</p> <p>Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)</p>	<p>Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.</p>
<p><b>Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)</b></p>	<p>Withhold avelumab therapy Consider hospitalization Endocrinology consult</p> <p>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate.</p> <p>Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)</p>	<p>Resume avelumab once symptoms and/or laboratory tests improve to Grade <math>\leq</math> 1 (with or without hormone replacement/suppression).</p> <p>Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.</p>
<p><b>Hypopituitarism/Hypophysitis (secondary endocrinopathies)</b></p>	<p>If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately</p>	<p>Resume avelumab once symptoms and hormone tests improve to Grade <math>\leq</math> 1 (with or without hormone replacement).</p> <p>In addition, for hypophysitis with abnormal</p>

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	<p>low ACTH):</p> <ul style="list-style-type: none"> <li>Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women)</li> <li>Hormone replacement/suppressive therapy as appropriate</li> <li>Perform pituitary MRI and visual field examination as indicated</li> </ul> <p><b>If hypophysitis confirmed:</b></p> <ul style="list-style-type: none"> <li>Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month</li> <li>Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month.</li> <li>Add prophylactic antibiotics for opportunistic infections.</li> </ul>	<p>MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.</p> <p>Continue hormone replacement/suppression therapy as appropriate.</p>
<b>Other irAEs (not described above)</b>		
<b>Grade of other irAEs (NCI-CTCAE v4)</b>	<b>Initial Management</b>	<b>Follow-up Management</b>
<b>Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE</b>	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
<b>Grade 2 irAE or first occurrence of Grade 3 irAE</b>	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.

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<p><b>Recurrence of same Grade 3 irAEs</b></p>	<p>Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate</p>	<p>If improves to Grade <math>\leq</math> 1: Taper steroids over at least 1 month.</p>
<p><b>Grade 4</b></p>	<p>Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.</p>	<p>If improves to Grade <math>\leq</math> 1: Taper steroids over at least 1 month</p>
<p><b>Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency</b></p> <p><b>Persistent Grade 2 or 3 irAE lasting 12 weeks or longer</b></p>	<p>Permanently discontinue avelumab therapy Specialty consult</p>	

Abbreviations: ACTH=adrenocorticotrophic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatinine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin; T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

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### **15.5 Attachment: 5**

#### ***Factors to Consider in Assessing the Relationship of AEs to Avelumab or Infusion Procedure, Study Procedure, or Combination Treatment***

Is there a reasonable possibility that the event may have been caused by the study drugs or infusion procedure, study procedure, or concomitant treatment?

**No:**

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's/subject's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of Avelumab, study procedure, or combination treatment
- do not reappear or worsen when dosing with Avelumab, study procedure, or combination treatment is resumed
- are not a known response to Avelumab or infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

**Yes:**

- could not be explained by environmental factors or other treatment/s being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of Avelumab
- resolve or improve after discontinuation of Avelumab, study procedure, or combination treatment
- reappear or worsen when dosing with Avelumab, study procedure, or combination treatment is resumed
- are known to be a response to Avelumab or the infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

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**15.6 Attachment: 6**

**Technical Specifications and Structural Considerations for  
Planning Radiotherapy**

**Technique:**

Intensity modulated radiotherapy (IMRT) via any method (e.g., VMAT, static field IMRT) or Stereotactic Radiotherapy (SRT) is required. Protons are permitted for institutions which have been approved and credentialed for protons, as protons may reduce the volume of normal tissue which will be re-irradiated. If protons are used, to avoid delays resulting from unplanned equipment availability, photon therapy may be administered instead of proton therapy.

**Every attempt must be made to obtain the original radiotherapy treatment plan in order to guide re-irradiation treatment planning.**

**Dose Specifications**

Photons: Treatment shall consist of 25 Gy delivered in 5 fractions delivered over 5 consecutive treatment days. The treatments may extend over the weekend (e.g., 5 treatment days over 8 calendar days.) Target coverage and homogeneity limits and deviations are listed in **Table A1**.

Protons - Absorbed dose: Doses are expressed in units of RBE-weighted absorbed dose,  $D_{RBE}$ . For protons the RBE is taken to be 1.1.  $D_{RBE} = 1.1 \times D$ , where D represents the absorbed dose in Gy. Treatment shall consist of 25 Gy(RBE) delivered in 5 fractions. Target coverage and homogeneity limits and deviations are listed in the **Table A1** below.

**Table A1: Target Coverage and Dose Limits**

<b>Dose Metric</b>	<b>Per Protocol</b>	<b>Variation Acceptable</b>	<b>Deviation Unacceptable</b>
Volume of PTV covered by the prescription dose of 25 Gy photons - protons 25 Gy(RBE)	Greater than or equal to 95% of the PTV should receive greater than or equal to 25 Gy photons - protons 25 Gy(RBE)	Greater than or equal to 90% of the PTV receiving greater than or equal to 25 Gy photons - protons 25 Gy(RBE)	Less than 90% of the PTV receiving greater than or equal to 25 Gy photons - protons 25 Gy(RBE). Coverage less than 90% is acceptable in areas of OAR/PTV overlap.
Minimum dose to the PTV (0.03 cc)	Greater than or equal to 21.25 Gy (85% of the prescription dose) photons – protons 21.25 Gy(RBE)	Greater than or equal to 20 Gy (80% of the prescription dose) photons – protons 20 Gy(RBE); Minimum doses of less than 20 Gy are acceptable if they occur due to OAR/PTV overlap	Less than 20 Gy (80% of the prescription dose) photons – protons 20 Gy(RBE); Minimum doses of less than 20 Gy are unacceptable unless they occur in regions of OAR/PTV overlap
Maximum dose to the PTV (0.03 cc)	Less than or equal to 30 Gy (120% Rx Dose)	Less than or equal to 32.5 Gy (130% Rx	Greater than 32.5 Gy (130% Rx Dose)

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	photons – protons 30 Gy(RBE). For SRT, this represents a plan prescribed to the 84% or greater Isodose line)	Dose) photons – protons 32.5 Gy(RBE). For SRT, this represents a plan prescribed to the 80% isodose line)	photons – protons 32.5 Gy(RBE) or an isodose line less than 80% for a radiosurgical plan)
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### Technical Factors (Equipment, Energies)

Intensity modulated radiotherapy (IMRT) via any method (e.g., VMAT, static field IMRT) or Stereotactic Radiotherapy (SRT) is required. Any FDA cleared external beam radiation delivery system may be used (including conventional linear accelerators, cyberknife systems, tomotherapy, proton therapy, etc.). Treatment at NYULMC will be on Varian LINAC (TrueBeam or Edge) or Elekta Gamma Knife Perfexion Unit.

Image-guided radiotherapy with cone-beam CT along with daily treatment kV/kV imaging will be performed daily.

Imaging for treatment planning will be obtained with the patient in the same position and immobilization device as for treatment. All patients will be positioned via a combination of rigid immobilization and daily image guidance to ensure positioning accuracy of 3 mm or better, and of a magnitude that justifies the PTV margin applied.

### Localization, Simulation, and Immobilization

MRI fusion with CT are required for treatment planning. At least 1 of these scans must be of the patient immobilized in treatment position, and with image resolution of no worse than 1.5 mm x 1.5 mm x 3 mm. MRI sequences should include axial T1 post-contrast stereotactic image (such as MP-RAGE or FSPGR BRAVO). Contrast may be omitted if medically indicated. Additionally, a T2 sequence (e.g., FLAIR or T2, preferably stereotactic, thin slice, contiguous) is helpful to identify any non-enhancing tumor.

Immobilization must be rigid (e.g., thermoplastic masks). For daily treatment, localization will include the steps of a) immobilization with the same device used for simulation, and b) daily image guidance using at a minimum orthogonal pairs of radiographs aligned to DRRs as a computer-assisted process. Daily cone-beam CT will be used as well.

### Treatment Planning/Target Volumes

A GTV will be defined using the CT and MRI images.

The GTV includes the post-operative resection cavity if no residual enhancing or non-enhancing tumor is noted. The GTV also includes any non-enhancing tumor as identified on T2/FLAIR. T2/FLAIR signal consistent with edema is not included in the GTV. Therefore a distinction is made between T2 edema (typically without mass effect, sparing the cortical ribbon, obeying the grey/white junction, etc.) with T2 tumor (mass effect with sulcal effacement, involvement of the grey/white junction, obliteration of the cortical ribbon). Care is made to not include any enhancement or T2 signal on the post-operative scan that is due to post-surgical infarct. Fusion of the pre-operative MRI to determine initial extent of the tumor is helpful.

A PTV expansion that is justified based on image guidance and immobilization will be applied. Regardless of immobilization and localization methods, the PTV expansion should be no larger than 3 mm. Therefore, for stereotactic treatment, the PTV is typically 1 mm. For non-stereotactic treatment with IGRT, then the PTV is typically 3 mm.

### Critical Structures

Normal tissues to be contoured will include the brain, brainstem, optic nerves and chiasm. Planning risk volume (PRV) expansions the same size as the PTV expansion (e.g. If the PTV is 3 mm, then the PRV is 3 mm. For stereotactic machines, a PTV of 0 mm is acceptable; therefore the PTV = CTV = GTV + 5 mm in this instance) should be utilized for optic nerves and chiasm.

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Special consideration should be given to avoid doses greater than the prescription dose within the scalp as well as limiting the exit dose through the oral cavity and mucosa.

The treatment parameters should be modified to optimize the conformity of the prescription isodose volume to the target volume while minimizing dose to critical structures. OAR limits for newly diagnosed GBM are given in **Table A2**.

**Table A2: Normal Dose Limits (5 Fractions)**

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
<b>Scenario (1): Previous radiation to the local area including critical organs at risk</b>			
Maximum Dose (0.03 cc) to PRV for Optic Nerves, Chiasm	Less than or equal to 20 Gy photons - 20 Gy(RBE) protons	Greater than 20 Gy but less than or equal to 25 Gy photons – 25 Gy(RBE) protons	Greater than 25 Gy photons - 25 Gy(RBE) protons
Maximum Dose (0.03 cc) to Brainstem	Less than or equal to 24 Gy photons - 24 Gy(RBE) protons	Greater than 24 Gy but less than or equal to 25 Gy photons – 25 Gy(RBE) protons	Greater than 25 Gy photons - 25 Gy(RBE) protons
<b>Scenario (2): No previous radiation to the local area or critical organs at risk</b>			
Maximum Dose (0.03 cc) to PRV for Optic Nerves, Chiasm	Less than or equal to 25 Gy (the prescription dose) photons - 25 Gy(RBE) protons	Greater than 25 Gy but less than or equal to 26.25 Gy (105 % of the prescription dose) photons – 26.25 Gy(RBE) protons	Greater than 26.25 Gy (105% of the prescription dose) photons – 26.25 Gy(RBE) protons
Maximum Dose (0.03 cc) to Brainstem	Less than or equal to 25 Gy (the prescription dose) photons - 25 Gy(RBE) protons	Greater than 25 Gy but less than or equal to 26.25 Gy (105 % of the prescription dose) photons – 26.25 Gy(RBE) protons	Greater than 26.25 Gy (105% of the prescription dose) photons – 26.25 Gy(RBE) protons

Coverage of the PTV will be decreased in order to fulfill these limits.

The optic structures (chiasm and optic nerves) are kept to <350 cGy per fraction and the brainstem is allowed a D05 (the dose encompassing 5% of volume) of 600 cGy per fraction so that no more than 5% of the brainstem receives 600 cGy per fraction.

Radiotherapy dose constraints are based on the radiation therapy dose specifications in RTOG 1205.

### Documentation Requirements

At the completion of treatment, the following should be forwarded to the overall Principal Investigator listed below. Investigators must submit the following information:

- Daily treatment record.
- Radiotherapy summary.
- Pre-study CT or MRI (the Scan used to delineate the target volumes for planning. Submit the entire series and specify which one was used for planning).
- Isodose distributions displayed on orthogonal planes or, if not possible, on multiple transverse slices through each target.

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Data should be submitted to:

Sylvia Kurz, MD, PhD  
Laura and Isaac Perlmutter Cancer Center  
NYU Langone Medical Center  
240 East 38th Street, 19th Floor  
New York, NY 10016

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## 15.7 Attachment: 7

### **Research Biomarker/Correlative Studies: Background and Rationale**

**Note:** This study involves collection of required archival tumor tissue and blood specimens for research as well as collection of an optional tumor specimen if a biopsy is required during or after protocol therapy. All patients will be given the option to have leftover research specimens after study completion and completion of protocol-defined research studies banked for future research at the time of informed consent. See **Section 9.1.1** for details on leftover research samples.

#### **A. Research Specimens to be Collected**

##### **1. Archival tumor tissue**

A paraffin-embedded or frozen tumor-tissue block with a minimum of 1 cm<sup>2</sup> of tumor surface area containing at least 20% viable tumor from a tissue specimen that demonstrates one of the two criteria specified below (also in **Inclusion Criteria 4a**). If a tumor block cannot be submitted, then 20 unstained 5-micron slides from the tumor specimen must be submitted.

(A) Histopathological evidence of glioblastoma (WHO grade IV) on a progressive tumor specimen after treatment with temozolomide or PCV chemotherapy. The diagnosis of glioblastoma must be confirmed on central review by a study-designated neuropathologist at NYU at screening.

or

(B) Any progressive glioma with *IDH1* or *IDH2* mutation, regardless of WHO grade or histopathological diagnosis, may be eligible contingent on approval by the overall Principal Investigator if the progressive tumor specimen is found to have one of the genetic alterations below:

1. ≥20 somatic mutations per Mb by whole-exome DNA sequencing
2. Mutation in a mismatch repair (MMR) gene or other genes known to be associated with hypermutator phenotypes or microsatellite instability, including but not limited to *MSH2*, *MSH6*, *MLH1*, *POLE*, *PMS2*, *POLD* as determined by validated methods.
3. Microsatellite instability (MSI) as identified by polymerase chain reaction (PCR) or other validated methods.

##### **2. (Optional) Tumor Biopsy**

If subjects undergo tumor resections or biopsies during the study period after treatment initiation, or after progression on HFRT + Avelumab, a tumor specimen will be collected for research purposes. A section of frozen tumor or a FFPE block (surface area of 1 cm<sup>2</sup> containing at least 20% viable tumor, as described above in Section 6.8.2) from the tumor surgery is preferred. If a frozen tumor specimen or a tumor block cannot be provided, then 20 unstained 5-micron slides (preferably 10 slides from two different tumor blocks from the same surgery) from the tumor block should be sent.

Send all research tumor specimens (archival and optional tumor biopsy) to:

Matija Snuderl, MD

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Department of Pathology, NYU Langone Medical Center  
560 First Avenue  
Tisch Hospital HW 451  
New York, NY 10016  
Phone: 646-501-5281, Fax: 212-263-7916, Pager: 917-205-5543  
Email: Matija.Snuderl@nyumc.org

### 3. Research Blood Samples

Research blood samples will be taken at only **2 timepoints**: Baseline (prior to Cycle 1, Day 1) and at Cycle 2, Day 1, as per the study procedures (**Section 6**) and the **Schedule of Events, Attachment 1**.

Refer to the study **Lab Manual** for specific processing, handling and shipping procedures for research blood specimens.

Research blood samples will be collected from all subjects as detailed below.

- **NYULMC subjects**: 40 mL (four 10 mL purple top EDTA tubes) of whole blood will be drawn and immediately sent to the below sites:
  - One (1) 10 mL tube will be sent to the Center for Biospecimen Research and Development (CBRD) at NYULMC for acquisition of whole blood, buffy coat, and plasma samples.
  - Three (3) 10 mL tubes will be sent to the Immune Monitoring Core (IMC) at NYULMC and immediately processed for isolation of PBMCs.
- **Subjects at other sites**: 30 mL of whole blood will be collected in two types of Streck tubes provided by NYULMC. All tubes will be shipped overnight to the CBRD at NYULMC per instructions in the **Lab Manual**. **\*Subsites should NOT schedule research blood draws on Fridays as the NYU CBRD will not be able to receive specimens on weekends.**
  - 10 mL will be drawn into one Streck Cell-Free DNA BCT® collection tube.
  - 30 mL total will be drawn into three 10 mL purple top EDTA tubes and immediately sent via overnight shipping to NYULMC. On arrival at NYULMC, the tubes will be sent immediately to the Immune Monitoring Core and immediately processed for isolation of PBMCs.

All blood samples from non-NYULMC sites should be sent to the CBRD at NYULMC at the address below, per instructions in the Lab Manual. Research blood specimens collected from NYULMC subjects will be transported immediately to either the CBRD or the IMC (address below) as described above. **\*Subsites should NOT schedule research blood draws on Fridays as the NYU CBRD will not be able to receive specimens on weekends.**

#### **Center for Biospecimen Research and Development (CBRD)**

NYU Langone Medical Center  
Medical Science Building  
550 First Avenue, Berg 3rd Fl., Rm. 381  
New York, NY 10016  
CBRDResearchRequest@nyumc.org  
1 (646) 501-4268

#### **The Immune Monitoring Core (IMC)**

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522 First Avenue  
Medical Science Building, MSB 367  
New York, NY 10016  
Debra.Morrison@nyumc.org

## B. Types of Planned Analyses

### I. Studies using Tumor Tissue Samples

- Whole-exome deep sequencing to assess hypermutation phenotype, estimation of the total mutation-associated neoantigens, and T cell receptor (TCR) diversity.
- RNA-Seq to assess expression of predicted mutation-associated neoantigens.
- Immunohistochemistry (IHC) to assess intratumoral PD-L1 expression
- IHC to determine tumor-infiltrating lymphocytes (TILs)

### II. Studies Using Blood Samples

- Flow cytometry for quantification of T<sub>reg</sub> and myeloid-derived suppressor cell (MDSC) levels
- Genomic DNA for paired tumor sequencing
- TCR deep sequencing to determine peripheral clonal T-cell expansion and TCR diversity
- Circulating tumor DNA analysis

## C. Specific Planned Analyses

### 1. Tumor Tissue Whole-Exome Deep Sequencing

**Objectives:** To assess the association between PFS6 and:

- A)** Presence of temozolomide-induced hypermutation phenotype;
- B)** Total predicted neoantigen load;
- C)** T cell receptor (TCR) diversity

**A) Hypermutation phenotype:** Patients with lower-grade *IDH* mutant gliomas (WHO grade II or III) that are treated with temozolomide or PCV chemotherapy and later proceed to have histopathologic transformation to GBM (WHO grade IV) nearly universally develop hypermutation phenotype within their tumors (see Background and Rationale, **Section 1.1**). Temozolomide and PCV chemotherapy therapy provide selection pressure for clones that have acquired mutations in mismatch repair (MMR) genes which then dominate subsequent recurrences and drive histopathological transformation to the highest grade (GBM, WHO grade IV). The hypermutation phenotype is a distinct signature consisting of mutations in MMR genes (80-90% of cases have *MSH6* mutation) and an extremely high mutation frequency (>30 mutations per Mb in hypermutant versus 1-2 mutations per Mb in non-hypermutant cases) with a striking preponderance of C:G>T:A transitions at CpC dinucleotides.<sup>27,33,34</sup> Non-hypermutant progressive *IDH* tumors typically harbor 30-80 nonsynonymous mutations, whereas hypermutant *IDH* mutant GBMs typically harbor between 1,000 - 3,000 nonsynonymous mutations.<sup>27,29,34</sup> Notably, these

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cases are not detectable using a standard five reference panel of microsatellite instability (MSI) markers recommended by the NCI.<sup>35</sup>

We will compare the association of hypermutation phenotype between tumors that achieve PFS6 and those that do not. We will analyze archival transformed GBM tissue from all patients with whole-exome deep sequencing and define hypermutation as  $\geq 20$  somatic, nonsynonymous mutations per Mb with a concomitant preference for C:G>T:A transitions at CpC dinucleotides. If enough archival tumor material is available, we will examine the clonality of hypermutated tumors through whole-exome sequencing of multiple spatially distinct tumor samples. If feasible, we will assess whether achieving PFS6 is impacted by whether hypermutation occurs subclonally or constitutes the majority of the recurrent tumor.

**B) Total predicted neoantigen load:** We will compare the potential mutation-associated neoantigen load between tumors that achieve PFS6 and those that do not. Using somatic exome data, we will assess the hypermutant cases for their immunogenic potential in the context of each patient's major histocompatibility complex (MHC) haplotype. To assess the potential for mutant peptide binding, somatic exome data combined with each individual patient's class I HLA haplotype will be applied to an epitope prediction algorithm,<sup>89,90</sup> which provides an estimate of the total number of mutation-associated neoantigens in each tumor.

**C) T cell receptor (TCR) diversity:** One strategy to reverse the suppression of tumor immune responses involves the use of radiation therapy (RT), which has been shown to augment anti-cancer immune responses and enhance the efficacy of immune therapies in systemic cancer preclinical models and patients.<sup>43-49</sup> Preclinical studies examining combined radiotherapy and checkpoint inhibition indicate that each activate mostly non-redundant immune stimulating mechanisms and the major contribution of radiotherapy appears to be increasing T-cell receptor (TCR) diversity.<sup>48</sup> RT induces major histocompatibility complex (MHC) class I presentation, increases antigen presentation, and increases cytotoxic T cell (CTL) recognition of irradiated cells<sup>50,51</sup> and enhances the diversity of the TCR repertoire of the expanded peripheral T cell clones.<sup>48</sup>

We will characterize the baseline pre-treatment intratumoral TCR diversity and use intratumoral TCR diversity data (e.g., the top 100 most frequent intratumoral TCR clonotypes) to examine TCR clonotype frequencies in pre-treatment (Baseline) and post-treatment (C2D1, 29 days post-initiation of Avelumab and 21 days after completion of HFRT) blood samples. Using combined tumor tissue and pre-treatment (baseline) blood, we will generate whole-exome sequencing data and analyze frequencies/counts of TCR clonotypes to estimate the TCR diversity. The Shannon's diversity index (DI)<sup>91</sup> normalized to the number of reads ( $DI = -\sum(\text{piln } \pi_i) / \ln n$ , where  $n$  is the number of clones,  $\pi_i$  is the clonal frequency of the  $i$ th clone, and sigma is summed from  $i = 1$  to  $i = n$ ) was calculated for each sample. This gives a value between 0 and 1, where 0 is monoclonal and 1 is an even distribution of different clones.

**If Post-treatment tumor tissue is available:** Additionally, if patients undergo tumor resections or biopsies during study therapy or after progression on HFRT + Avelumab, we will whole-exome sequence multiple spatially distinct regions, if possible, of the progressive tumor to determine whether alterations in the clonal hypermutation distribution, TCR clonotype distribution or predicted neoantigens have occurred.

## 2. Tumor Tissue RNA-Seq

**Objective:** To use tumor tissue RNA-Seq data to evaluate the fraction of predicted mutation-associated neoantigens derived from somatic whole-exome sequencing data that is expressed and assess the association of PFS6 and number of expressed mutation-associated neoantigens.

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**Expression of predicted mutation-associated neoantigens:** We will estimate the proportion of predicted mutation-associated neoantigens that are expressed by RNA-Seq and compare the expressed predicted mutation-associated neoantigen load between tumors that achieve PFS6 and those that do not. Total RNA will be extracted from FFPE tumor tissue using RNA extraction kits, treated to remove genomic DNA, quantified, and analyzed for integrity. RNA-Seq libraries will be prepared using standard protocols to purify poly-adenylated mRNA, generate double-stranded cDNA and ligate adapters and then submitted for next-generation sequencing

**Clonality of mutation-associated expressed neoantigens:** If enough tumor tissue is available to assess distinct regions of an individual tumor, we will perform RNA-Seq analyses on different regions of each tumor to assess the clonality of expressed neoantigens.

### 3. Tumor Tissue Immunohistochemistry (IHC)

**Objectives:** To assess the association of PFS6 and:

- A) Tumor tissue PD-L1 expression,
- B) baseline density and subtype of TIL populations.

**A) Tumor cell programmed death-ligand 1 (PD-L1) expression:** We will assess the association of PFS6 with baseline membranous and diffuse tumor cell PD-L1 expression. Tumor PD-L1 has been associated with response to PD-1 inhibitor therapy in studies of other solid cancers (see Rationale and Background, **Section 1.1**) however the association of tumor tissue PD-L1 expression and response to anti-PD-1 or anti-PD-L1 therapy is unknown.

IHC staining of paraffin-embedded sections for PD-L1 will be performed on archived formalin-fixed paraffin-embedded archival tumor specimens as previously described.<sup>15</sup> The IHC assay for PD-L1 will incorporate an anti-PD-L1 rabbit monoclonal antibody (clone 28-8), which was developed on an automated platform by Dako North America. Consecutive sections will be stained for PD-L1 and a negative control reagent to control for nonspecific staining. A sample will be deemed PD-L1 positive for membranous staining if  $\geq 5\%$  of tumor cells, in a minimum of 100 evaluable tumor cells, have observable PD-L1-positive staining at any intensity. Specificity of the 28-8 antibody clone has been extensively validated previously.<sup>15</sup>

In addition, we will explore the association of T<sub>reg</sub> (CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>) levels in tumor tissue and in circulation at baseline. Circulating T<sub>reg</sub> levels will be quantified as below, and tumor tissues will be stained for CD4 and FoxP3 to assess infiltrating T<sub>reg</sub>s.

**B) Tumor Infiltrating lymphocytes (TILs):** We will assess the density and subtype of TILs in baseline pre-treatment FFPE tumor tissue by IHC using markers such as CD3, CD4, CD8, CD56, FoxP3, and PD-1.

**If Post-treatment tumor tissue is available:** Additionally, if patients undergo tumor resections or biopsies during study therapy or after progression on HFRT + Avelumab, we will assess for changes in tumor tissue PD-L1 expression and TIL density and subtype after treatment with Avelumab + HFRT.

### 4. Peripheral Blood Flow Cytometry

**Objectives:** To assess the association of PFS6 and baseline level of T<sub>regs</sub> or MDSCs within PBMCs or their change at 4 weeks from Avelumab initiation

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**Circulating T<sub>regs</sub> and MDSCs in PBMCs:** We will test whether the baseline level of circulating regulatory T cells (T<sub>regs</sub>) or myeloid-derived suppressor cells (MDSCs) within peripheral blood mononuclear cells (PBMCs) or their change at 4 weeks from Avelumab initiation (C2D1, also 21 days after completion of HFRT) are associated with PFS6. In GBM patients, T<sub>reg</sub> and MDSC populations have been reported to facilitate tumor immune evasion. T<sub>regs</sub> have been found an increased fraction of the circulating CD4 compartment in GBM patients and correlates with proliferative defects among CD4<sup>+</sup> T cells.<sup>92</sup> MDSCs are a heterogeneous group of immature myeloid-derived cells that are capable of suppressing the immune system and are increased in the blood and tumor tissue of patients with various tumors. Recently, MDSCs were found to be increased in the blood of GBM patients compare to healthy controls, while a subset of MDSCs [polymorphonuclear MDSCs (PMN-MDSCs)] were highly prevalent in GBM tumor tissue.<sup>93</sup>

All subjects will have research blood drawn at baseline and 4 weeks post-Avelumab initiation for flow cytometry studies. 30 mL of (EDTA purple top tube) whole blood will be drawn and immediately processed at the study sites using Ficoll technique for isolation of PBMCs. Processed study samples will be frozen and stored until shipment to NYULMC for analysis. In melanoma patients treated with nivolumab, T<sub>regs</sub> decreased in responders and stable patients and significantly increased in non-responders at 12 weeks.<sup>15</sup> At the Immune Monitoring Core at NYULMC, PBMCs will be thawed and analyzed by flow cytometry. Functional and phenotypic markers of T cells will be evaluated by flow cytometry using antibodies from BD Biosciences, except where indicated. PBMCs will then be stained with Live/Dead violet dye (Invitrogen) to gate on live cells. Then, cells will be assessed for expression of CD45, CD3, CD4, CD8, PD-1 (MIH4 from eBioscience), and CTLA-4.

T<sub>regs</sub> will be defined as cells with CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>low</sup>FoxP3<sup>+</sup> (eBioscience). MDSCs will be defined as MHC class II negative, CD33<sup>+</sup>, CD15<sup>+</sup> cells as previously described.<sup>93</sup> Cells will be assessed for expression of CD33, HLA-DR, -DP, -DQ and CD15 (Becton Dickinson). Data will be acquired on an LSR II flow cytometer (BD Biosciences) and analyzed with Flowjo software (TreeStar).

## 5. Peripheral Blood Deep Sequencing

**Objectives:** Peripheral blood will be collected for deep sequencing for the purposes of:

- A) Sequencing normal (germline) DNA to identify tumor somatic mutations
- B) Assessing for alterations in TCR clonotype frequencies in pre-treatment and post-treatment blood,
- C) Exploring the potential of identifying circulating tumor DNA in patients with *IDH* mutant gliomas.

**B) TCR clonotype frequencies (All subjects):** We will determine whether treatment with HFRT and Avelumab results in peripheral expansion of TCR clonotypes found in TIL clones identified by tumor tissue whole-exome sequencing and alters the TCR repertoire of the most expanded TCR clonotypes. Previous studies indicate radiotherapy and immune checkpoint inhibition activate non-redundant immune mechanisms and the major contribution of radiotherapy may be increasing TCR diversity and shaping the TCR repertoire of the expanded peripheral T cell clones.<sup>48</sup> DNA will be extracted from peripheral blood cells and analyzed with whole-exome deep sequencing to analyze frequencies/counts of the top 100 most frequent TCR clonotypes identified in baseline tumor tissue.

**C) Circulating tumor DNA in patients with *IDH* mutant gliomas:** In nearly all cases that have been reported, the mutant *IDH* allele is ubiquitous throughout the tumor mass. In addition, in nearly every case reported in gliomas the mutant *IDH* allele is heterozygous with the wildtype allele and genetic amplification has never been reported. Therefore, the mutant *IDH* allele represents an attractive diagnostic and pharmacodynamic biomarker. We will sequence cell-free

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fractions of blood to high depths to attempt to detect circulating mutant *IDH* allele and also attempt to compare the changes in the allele fraction between baseline and post-treatment blood.

All subjects will have research blood drawn at baseline and 4 weeks post-Avelumab initiation (C2D1, 29 days post-initiation of Avelumab and 21 days after completion of HFRT). 10 mL of whole blood in EDTA tubes (purple top tubes) will be drawn at each timepoint and processed according to the study **Lab Manual**. From the whole blood sample, a 1mL aliquot will be immediately taken and frozen separately in a cryovial. The remaining sample will be spun to separate the plasma, buffy coat, and cells. The buffy coat and plasma will each be separated and placed in cryovials for freezing. Samples will be batch-shipped to the **NYULMC Center for Biospecimen Research and Development (CBRD)**. DNA will be extracted and analyzed with whole-exome deep sequencing to analyze frequencies/counts of the top 100 most frequent TCR clonotypes identified in baseline tumor tissue.

## Statistical Considerations for Correlative Studies

Correlative biomarker endpoints are exploratory and hypothesis generating. The correlative studies are not powered to make a formal test of the prognostic power of any biomarker. We will use non-parametric statistics (e.g. Wilcoxon, Spearman's rank correlation coefficient, Fisher's Exact test) to test the association between presence of temozolomide-induced hypermutation and PFS6 as well as the fraction of predicted mutation-associated neoantigens, fraction of expressed mutation-associated neoantigens, and levels of tumor-infiltrating immune populations identified by RNA-Seq between patients that achieve PFS6 and those that do not.

For the circulating Treg and MDSC biomarker study, we summarize the distributions of levels at baseline and changes from baseline at Day 35 using descriptive statistics and graphical displays. Changes from baseline will be examined using Wilcoxon signed rank tests for paired measurements. Logistic regression will be used to predict PFS6 (binary) based on baseline levels and the changes from baseline. Optimal cutpoints for changes from baseline will be estimated for the separation of those patients who are alive and free of progression at 6 months compared to those who are not using the Youden Index based on the receiver operating characteristic curve.

For the tumor tissue PD-L1 and TIL assays, we will use similar descriptive analyses and summary displays to assess whether expression of PD-L1 is associated with PFS6. Additional analyses will combine all of these key biomarkers in logistic models to identify potential combinations of markers to predict PFS6.

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