CLINICAL STUDY PROTOCOL – CONFIDENTIAL

PROTOCOL TITLE: **Avelumab in patients with newly diagnosed Glioblastoma Multiforme**

DATE & VERSION: December 02, 2020
Version 5

STUDY SPONSOR: Clinique Neuro-Outaouais

STUDY DRUG and INDICATION: Avelumab, glioblastoma multiforme

TYPE OF STUDY: Phase 2, single center, open ended, open label addition of avelumab to standard therapy

CO-AUTHORS: Dr François Jacques, Dr Garth Nicholas, Ian Lorimer PhD

INSTITUTION:

Clinique Neuro-Outaouais
209, Rue Gamelin
Gatineau, Quebec, Canada

Phone: 819-777-2500
email: francois.jacques@neuro-outaouais.ca

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I. CONTACTS LIST

Principal Investigator
Name: Dr Francois Jacques
Clinique Neuro-Outaouais
209, Rue Gamelin, suite 200
Gatineau, Québec J8Y 1W2
Phone: 819-777-2500 Fax: 819-777-2502
E-mail: francois.jacques@neuro-outaouais.ca

Study Coordinators
Name: Victorine Sikati-Foko
Phone: 819-777-2500 Fax: 819-777-2502
E-mail: victorine.sikatifoko@neuro-outaouais.ca

Name: Nathalie Dumais
Phone: 819-777-2500, Fax: 819-777-2502
E-mail: nathalie.dumais@neuro-outaouais.ca

II.GLOSSARY OF ABBREVIATIONS

5-ALA	5-Aminolevulinic acid
5-FU	5-Fluorouracil
ACCP	American College of Chest Physicians
ADCC	Antibody Dependent Cellular Cytotoxicity
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
β-HCG	Beta-Human Chorionic Gonadotropin
BOR	Best Overall Response
BP	Blood pressure
BUN	Blood Urea Nitrogen
CALGB	Cancer and Leukemia Group B
CCL2	Chemokine ligand 2
CI	Confidence interval
CR	Complete Response
CRF	Case Report Form(s)
CSR	Clinical Study Report
CT	Computed Tomography
CTLA-4	cytoxic T-lymphocyte antigen-4
CTV	Clinical Tumor Volume
CNS	Central Nervous System
CVAD	Central Venous Access Device
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
DVH	Dose-Volume Histograms
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EEG	Electroencephalogram
EGFR	Epidermal Growth Factor Receptor
EIAEDs	Enzyme-inducing Antiepileptic Drugs
EORTC	European Organization for Research and Treatment of Cancer
ePD	Early Progressive Disease
ESMO	European Society for Medical Oncology
ESF	Eligibility Screening Form
EU	European Union
FASL	FAS ligand
GBM	Glioblastoma
GCP	Good Clinical Practice

G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GI	Gastrointestinal
GTV	Gross Tumor Volume
Gy	Gray
H0	Null hypothesis
H1	Alternative hypothesis
IC	Informed Consent
ICH	International Conference on Harmonization
ICRU	International Commission on Radiation Units and Measurements
IDH	isocitrate dehydrogenase gene
IHC	Immunohistochemistry
Il-2	Interleukin-2
IL-6	Interleukin-6
Il-10	Interleukin-10
INR	International Normalized Ratio
IMP	Investigational Medicinal Product
IMRT	Intensity-Modulated Radiation Therapy
irAEs	Immune –Related Adverse Events
irRC	Immune-related Response Criteria
iRANO	Immunotherapy Response Assessment in Neuro-Oncology
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRF	Independent Review Facilities
ISH	In situ hybridization
ITT	Intent To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
KPS	Karnofsky performance Status
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
MGMT	O6-methylguanine-DNA methyltransferase
MMSE©	Mini Mental State Examination
MoAb	Monoclonal Antibody
MRI	Magnetic Resonance Image
mRNA	Messenger RNA
MTD	Maximum Tolerated Dose
muMAb	Murine Monoclonal Antibody
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base
NCF	Neurocognitive Function
NCI	National Cancer Institute (USA)
NCIC	National Cancer Institute of Canada
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
NCIC-CTG	National Cancer Institute of Canada Clinical Trials Group
NSAID	Non-steroidal Anti-Inflammatory Drug
NSCLC	Non-small Cell Lung Cancer
NYHA	New York Heart Association

OR	Overall Response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive disease or Pharmacodynamics
PD-1	programmed death 1 (receptor)
PD-L1	programmed death ligand 1
PE	Pharmacoeconomic
PFS	Progression free survival
PICC	Peripherally Inserted Central Catheter
PK	Pharmacokinetic
PlGF	Placental Growth Factor
p.o.	Oral administration
PR	Partial Response
PS	Performance Status
psPD	Pseudo progression
PT	Prothrombin Time
PTV	Planning Tumor Volume
q.d.	Once daily administration
q.w.	Once a week
q2w	Once every 2 weeks
q3w	Once every 3 weeks
RCR	Roche Clinical Repository
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RPA	Recursive Partitioning Analysis
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	Serious Adverse Event
SD	Stable Disease
SNP	Single Nucleotide Polymorphism
SPD	Sum of the Product of biperpendicular Diameters of the measurable enhancing lesions
SRS	Stereotactic Radiosurgery
SWFI	Sterile Water for Injection
T1/2	Half-life
t.b.d.	To be determined
TE	Tracheoesophageal
TEAE’s	Treatment Emergent Adverse Events
TGF-B	Transforming Growth Factor
TMA	Tissue Microarray
TMZ	Temozolomide
TO	target occupancy
Treg	regulatory T cell
TTP	Time to Tumor Progression
ULN	Upper Limit of Normal

UPC	Urine Protein/Creatinine Ratio
USP	United States Pharmacopeia
Vc	Volume of the Central Compartment
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

III. SYNOPSIS OF PROTOCOL

Version Number: 5

Protocol Title: Avelumab in patients with newly diagnosed Glioblastoma Multiforme

Sponsor: Clinique Neuro-Outaouais

Indication: Patients with newly diagnosed Glioblastoma Multiforme

Study Type: Single center, phase 2, open-ended, open label, addition of avelumab to standard therapy

Objectives

Primary Objectives:
To determine the safety and tolerability of avelumab administered as 10mg/kg IV q2weeks in patients receiving standard therapy for newly diagnosed GBM.

Secondary objectives:
To determine the impact of the addition of avelumab at a dose of 10mg/kg IV Q2weeks in patients receiving standard therapy for newly diagnosed GBM on overall survival (OS), progression free survival (PFS) and other antitumor activity parameters according to the immunotherapy Response Assessment for Neuro-Oncology (iRANO) (1) at 52 weeks and every 52 weeks thereafter.

Exploratory objectives:
To explore biomarkers that could predict treatment response to avelumab such as: the tumor immunoscore, presence and extent of PD-L1 expression on tumor cells and microglia/macrophages within the tumor

To correlate the OS and PFS in relation to the baseline value and the change from baseline to week 52 visit and every 52 weeks /or end of study visit (depending on whether the latter occurs before or after week 260) neurocognitive function as measured by the evoked potential P300 (normal), the baseline corticosteroid dose, the total cumulative corticosteroid dose over the whole study duration, the total cumulative temozolomide dose per BSA since diagnosis and the presence and severity of immune related adverse events (irAE's).

To assess and compare above mentioned biomarkers in tissue samples from patients with second surgical resection ie treatment failures.
To assess in this GBM population the duration of pseudoprogression and the lagtime needed for immunotherapy to become effective.

Study Design: This is a single center, phase 2, open-ended, open label, add-on, single dose study in patients receiving standard therapy for newly diagnosed GBM with

a projected duration of 5 years (260 weeks). In total 30 patients who meet the entry criteria will be entered into the study within 3 weeks of finishing their last day of combined radiotherapy/temozolamide. Avelumab will be initiated concurrently with the initiation of the first 5 days, monthly cycle of temozolamide and continued until the occurrence of a termination event defined as one of the following: 1) clinical evidence of neurological deterioration resulting in an ECOG score of at least 3 or more, unexplained by other comorbities, unchanged by an increase in corticosteroid dose and sustained for at least two weeks or 2) treatment emergent adverse event (TEAE) of grade 3 or more or 3) withdrawal of patient consent.

A local pathology report will constitute adequate documentation of histology for study inclusion.
The tumor block used for diagnosis of GBM must be collected for each patient and sent for MGMT assessment (if not already done), biomarker and immunoscore analysis. The availability of these samples is mandatory for the baseline visit.

Paraffin embedded blocks containing formalin-fixed tumor tissue representative of the glioblastoma diagnosis is the preferred sample (if available, and of sufficient quality), otherwise, a partial tumor block, or pathology material should be sent. If surgery was not performed but biopsy was performed (or if it is not possible to send FFPE tumor tissue blocks) at least 10 unstained, uncovered slides must be sent.

The study will consist of 3 different phases: a Combination Phase, a Monotherapy Phase and an Extended Safety Follow-up Phase

Combination Phase: Upon completion of the standard combination therapy of radiotherapy (total dose 60 Gy, administered as daily 2Gy fractions, 5 days/week or as per local protocol) and temozolomide (75 mg/m2/day p.o. qd) and a treatment break of no more than 21 days, the combination phase will start. Patients will receive temozolomide and avelumab for 6 cycles of 28 days each. During the 1st cycle Temozolomide will be given the first 5 days at a dose of 150mg/m2/day p.o. In the next cycle, the temozolomide dose should be escalated to 200/mg/m2 if permitted by the patient's hematological and non-hematological toxicity profile (as per NCI-CTC AE version 5). The temozolomide dose will be adjusted according to hematological and non-hematological toxicity as per temozolomide's product monograph (appendix 4). Avelumab will be administered on day 1 and day 15 of each cycle at a dose of 10mg/kg IV. Avelumab therapy will be withheld according to the occurrence and severity of avelumab emergent adverse events as per table 3. Patients will continue the combination of temozolomide (150-200mg/m2 per day PO X5 days Q28days) and avelumab (at 10mg/kg dose, IV on days 1 and 15 per cycle) until 6 cycles are completed or until the occurrence of a termination event.

Monotherapy Phase: Upon completion of the Combination Phase or upon stopping temozolomide because of temozolomide related toxicity/tolerability issues or patient choice, the patient will continue into the avelumab Monotherapy Phase. Avelumab 10mg/kg IV Q2weeks will be continued as monotherapy until the occurrence of a termination event.

Patients who experience irAE's may according to table 3 directives have their avelumab therapy suspended.

The use of Bevacizumab or re-irradiation will not be allowed in the study and will be considered as evidence of disease progression.

Patients will be promptly informed upon confirmation of disease progression as per the new iRANO criteria. They will be offered to pursue with the avelumab therapy as monotherapy or in combination with other therapies or to withdraw from therapy and enter the extended safety follow up phase. They will need to be reconsented before allowed to continue with the avelumab therapy.

Extended Safety Follow-up Phase:
Patients who discontinue avelumab therapy for any reason at any point in the study will be entered into an extended safety follow-up period of 90 days. Treatment will then be at the investigator or local oncologist's discretion. All subjects will be observed for the possible occurrence of delayed irAE's. Survival data and information about subsequent therapies will be collected. Tissue samples in patients undergoing second surgical resections will be obtained for further biomarker analysis.

Number of Subjects: 30 patients

Target population: patients with newly diagnosed GBM who will be undergoing standard temozolomide/radiotherapy followed by 6 cycles of temozolomide.

Inclusion criteria:

1. Signed informed consent
2. Age ≥ 18 years
3. Present with newly diagnosed supratentorial Glioblastoma (GBM) with a tissue diagnosis that has been established following either a surgical resection or biopsy. This includes treatment-naïve (chemotherapy and radiotherapy)- patients with prior diagnosis of a lower grade astrocytoma that has been upgraded to a histologically verified GBM
4. Karnofsky performance score of 70 or higher
5. Patients entering the study must be on a stable dose of no more than 12 mg (maximum) of Dexamethasone (or equivalent) daily for symptoms related to cerebral edema.
6. Will be or is undergoing or has received the standard therapy of chemo radiation therapy (60Gy in 30 fractions of 2Gy/day with concurrent temozolomide of 75mg/m2 per day PO or as per local practise) no more than 21 days ago
7. Has not yet begun but will begin standard monthly temozolomide therapy
8. Patient must have at least 1 formalin fixed paraffin embedded tumor tissue block representative of glioblastoma available for biomarker analysis and determination of MGMT status (if not already done). If tumor block is not available or not of adequate quality, sufficient pathology material, representative of glioblastoma, must be available

9. Adequate hematological function defined by absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused)
10. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤ 2.5 × ULN for all subjects
11. Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
12. Negative serum pregnancy test at screening for women of childbearing potential
13. Highly effective contraception for both male and female subjects if the risk of conception exists. (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required at least 28 days prior, throughout and for at least 30 days after avelumab treatment.
14. International normalized ratio (INR) or PT (secs) and activated partial thromboplastin time (aPTT):
    – in the absence of therapeutic intent to anticoagulate the subject:
    INR≤1.5 or PT ≤1.5 x ULN and aPTT ≤1.5 x ULN
    – in the presence of therapeutic intent to anticoagulate the subject:
    INR or PT and aPTT within therapeutic limits (according to the medical standard in the institution)
    NOTE: Use of full-dose anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to baseline visit.
15. Willing and able to comply with the protocol as judged by the Investigator

Exclusion Criteria:

1. Patients who have evidence of leptomeningeal disease,
2. Known significant pulmonary, cardiovascular, hepatic disorders or any other disease that in the opinion of the investigator would be contraindicated to receive anti PD-L1 therapy such as avelumab,
3. "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 (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication."

4. Prior treatment with bevacizumab or any checkpoint immune blockade therapies
5. Any other concomitant immunosuppressant other than temozolomide and steroids or any recent (within 3 months) experimental therapy,
6. Patients who have finished their radiotherapy course more than 3 weeks prior to baseline,
7. Prior organ transplantation, including allogeneic stem-cell transplantation
8. Significant acute or chronic infections including, among others:

- Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS),
- Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive),

9. Active autoimmune disease requiring ongoing immunosuppressant therapy that might deteriorate when receiving an immunostimulatory agent:

    - Subjects with diabetes type I, vitiligo, psoriasis, hypo or hyperthyroid disease or any other autoimmune disease not requiring immunosuppressive treatment are at the investigator's discretion eligible

    - Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day

    - Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable

10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma),
11. Pregnancy or lactation,
12. Known alcohol or drug abuse,
13. Any psychiatric or cognitive condition that would prohibit the understanding or rendering of informed consent,
14. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines.
15. Any other malignancy within 5 years prior to baseline, except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix
16. Evidence of any active infection requiring hospitalization or IV antibiotics within 2 weeks prior to baseline
17. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
18. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, 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.

Investigational Product: Dose/Route/Regimen:

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody (calculated molecular weight of 143832 Dalton) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1.

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 IV infusion at a dose of 10mg/kg IV Q2weeks.

Premedication: In order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusion of avelumab is mandatory (for example, 25 50 mg diphenhydramine and 500-1000 mg paracetamol IV or oral). *Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.*

Setting: Avelumab should be administered in a setting that allows for immediate access to an emergency 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 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Observation period: Following avelumab infusions, patients must be observed for 2 hours post infusion for potential infusion related reactions. The observation period will be reduced to 30 minutes after the 4 th infusion.

Safety Assessments:

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events
(SAEs), measurement of protocol-specified haematology, chemistry, and urine analysis variables; measurement of protocol specified vital signs; clinical assessments and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Only clinically significant laboratory abnormalities that require active management (i.e. those that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.) will be recorded as AEs or SAEs.

All assessments will be scheduled as indicated in the schedule of assessment tables. Additional assessments may be performed as clinically indicated. Adverse events will be graded according to NCI-CTC AE, version 5.0.

Routine laboratory assessments:

Laboratory tests including haematology, blood chemistry and urine analysis will be performed at screening and baseline and then Q2weeks prior to each avelumab dose and at the end of treatment visit and at 30 days post-treatment in the extended safety follow-up phase.

Urine pregnancy test for women of childbearing potential must be performed at baseline and least every month during treatment.

Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).

Hematology
Haemoglobin, platelet count, WBC count, absolute neutrophils and lymphocytes counts

Coagulation (at screening and baseline only)
INR or PT (secs), and aPTT

Blood Chemistry
Including total bilirubin, AST, ALT, LDH, GGT, alkaline phosphatase, albumin, serum creatinine, and electrolytes (sodium, potassium, calcium), amylase, lipase, glucose, ck, phosphate

Endocrinology
Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment

Urinalysis
Routine urine analysis by dipstick

Clinical assessments
A general physical and neurological exams will be performed at screening, baseline and then monthly during the first 3 months of the study then Q3months and at the end of avelumab treatment and 30 days after the last treatment.
Vital signs will be done at screening, baseline and before and during each infusion of avelumab
Pre-infusion questionnaire will be administered by the infusion nurse prior to every infusion of avelumab

Radiological assessment
MRI or CT scan will be performed as per local standard of care (ie Q3-4 months).
Study specified gadolinium enhanced MRI or CT scan for efficacy measures of the brain will be done at baseline and Q52weeks or in case of premature withdrawal at end of study visit at the investigator‘ discretion.

Electrophysiological assessment
A P300 evoked potential will be obtained at baseline and every 52 weeks /or end of study visit (depending whether the end of study occurs prior or after the week 260 visit) for all patients. The P300 will be done in lieu of cognitive assessment. The baseline value and its change will be correlated with clinical outcomes.

Endpoints
Complete data analysis will be done when all patients have completed the week 52 visit and repeated every 52 weeks thereafter.
Interim descriptive analyses will be done when the first 10 patients have completed week 52 visit and repeated when the first 20 patients have do so as well.

Primary:

Safety and tolerability based on avelumab related adverse events leading to permanent or transient discontinuation of avelumab
Treatment related adverse events of special interest will include those of autoimmune origin (irAE).
The adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

Secondary:

Radiological tumor response will be graded according to the Immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria by a single study radiologist based on the gadolinium enhanced brain MRI or CT scan performed at the study center at baseline and Q52 weeks or within 2 weeks of the end of study visit and the evaluations of locally obtained MRI's or CT scan.
Clinical tumor response as per the iRANO criteria will be evaluated by the principal investigator based on the protocol specified neurological exams
The OS and PFS will be stratified according to MGMT status, baseline age (>50yrs), baseline Karnofsky performance score (score of 100), whether the patient had a radical tumor resection vs biopsy and according to histopathological diagnosis of primary versus secondary GBM

Changes in the daily corticosteroid dose will be discouraged during the 2 week period prior to the week 52 or end of study MRI or CT scan.

Exploratory:

The correlation between OS and PFS and the prevalence of PD-L1 expression on tumor cells and microglia/macrophages within the tumor, the histological immunoscore.
The correlation between OS and PFS in relation to the baseline corticosteroid dose, the total cumulative corticosteroid dose over the whole study duration, the total cumulative temozolomide dose per BSA since diagnosis, the baseline value and the change from baseline to week 52 and every 52 weeks /or the end of study visit neurocognitive function as measured by the evoked potential P300 and the incidence and severity of irAE's.

The change between baseline biomarker results and those obtained from biomarkers in tissue samples from patients with second surgical resection i.e., treatment failures

Statistical Analysis:

Sample Size Considerations
A convenience sample of thirty (30) patients is based on recruitment feasibility. This sample size will permit estimation of dichotomous outcome rates with margins of error of less than 18% (based on a significance level of 0.05) and estimation of continuous parameter means to within 0.36 standard deviations. This is an early stage study, so analysis will focus on descriptive statistics. Continuous parameters will be summarized by means and 95% confidence intervals or by medians and interquartile ranges, as appropriate. Dichotomous outcomes will be summarized with point estimates of the rate, as well as 95% confidence intervals. Time-to-event data will be summarized using Kaplan-Meier curves.

Analyses
Complete analysis will be done when all patients have completed week 52 visit and repeated every 52 weeks thereafter. Interim descriptive analyses will be done when the first 10 patients have completed week 52 visit and repeated when the first 20 patients have done so as well.

Efficacy data

Primary Endpoints
Safety and tolerability based on drug related events leading to permanent or transient discontinuation.

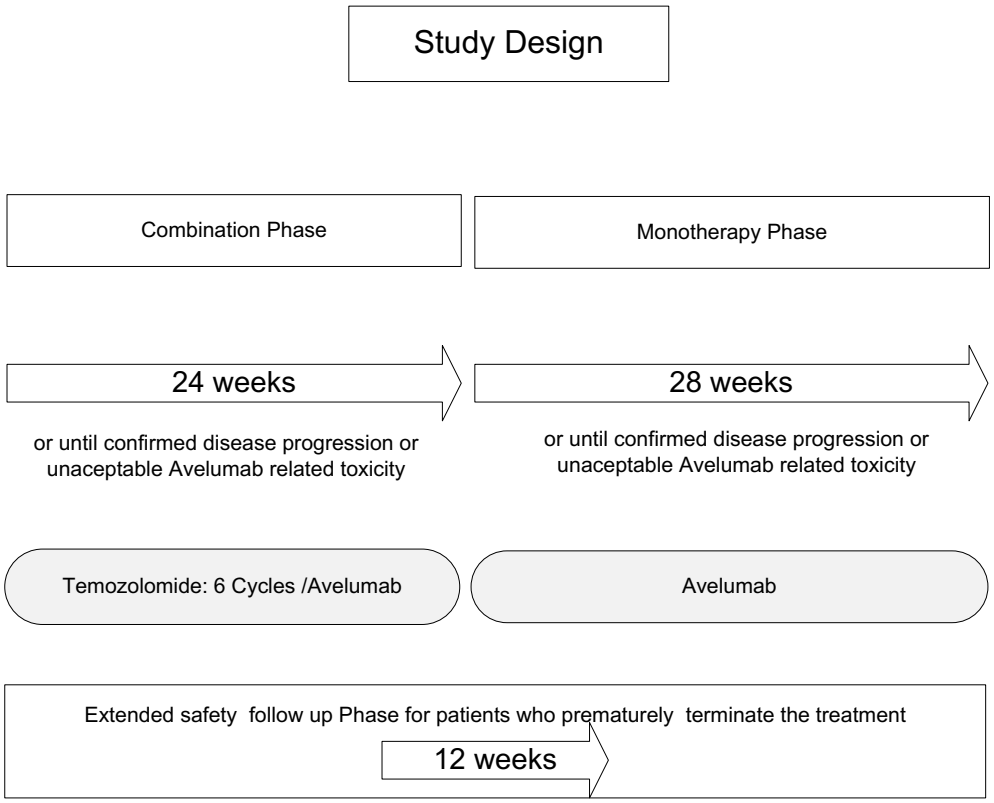
Secondary Endpoints

Radiological and clinical tumor response will be graded according to the immunotherapy Response Assessment for Neuro-Oncology (iRANO).
Results will be stratified according to the MGMT status, baseline age (>50yrs), baseline Karnofsky performance score (score of 100), radical tumor resection versus biopsy, primary versus secondary GBM.

Tertiary Endpoints

The prevalence of PD-L1 on tumor cells and microglia and the histological immunoscore in patients will be determined on tissue samples and their correlation to clinical response will be assessed.
The correlation between the OS, PFS, and other iRANO endpoints to the baseline corticosteroid dose, the total cumulative corticosteroid dose over the whole study duration, the total cumulative temozolomide dose per BSA since diagnosis, the baseline value and the change from baseline to week 52 and every 52 weeks /or the end of study visit neurocognitive function as measured by the evoked potential P300 and the incidence and severity of irAE's.

IV. STUDY FLOW CHART



The Monotherapy phase will continue until a termination event

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1. Background

1.1.1 Glioblastoma

Glioblastoma Multiforme (GBM) is the most common malignant primary brain tumor. It represents a WHO grade 4 glioma. It has an annual incidence of 3-5/100,000. It shows a slight predominance for males and a peak incidence between the fifth and sixth decades but can occur at any age. (1) Without treatment the 1 and 5 year survival is 29% and 3 % respectively (2).
Despite standard therapy of maximum resection followed by concurrent radiotherapy (60Gy) and temozolamide followed by 6, 5day, monthly cycles of temozolomide (TMZ) the median survival is 15 months and the 2-year survival, 27% (3). Recurrence of GBM usually occurs within a few months.
Recent phase 3 trials looking at escalating the radiotherapy dose beyond the 60Gy, increasing the dose of TMZ as adjuvant or maintenance therapy (8) or the addition of cilengitide (9) or bevacizumab (10) did not improve overall survival (OS).

Prognostic Factors

Mutations of the isocitrate dehydrogenase gene (IDH) 1 or 2 are hallmarks of low- grade glioma. When found in GBM (5 to 10% incidence) they suggest a secondary transformation i.e. secondary GBM and portend a better prognosis independent of MGMT methylation (4).
Methyl-guanine methyl transferase (MGMT) is involved in DNA repair. Its epigenetic silencing by gene promoter methylation leads to a greater vulnerability of the GBM to alkylating chemotherapy induced DNA damage (5). The improved outcome in GBM patients with methylated MGMT has been demonstrated repeatedly (6). MGMT methylation in patients with GBM (35% incidence) undergoing standard therapy conferred a definite survival advantage with 62% 18-month survival compared to 8% (7).
Other prognostic factors include radical resection, younger age (<50years), good performance status and an intact neurological function.

Practice guidelines

Recent ESMO practice guidelines (11) suggest that all GBM patients should undergo MGMT methylation status and IDH determination. Patients that are MGMT methylation (+) and those that are IDH (+) should undergo the standard TMZ/RT followed by TMZ protocol while those that are (-) should be considered for investigational protocols. Frail or elderly patients that are MGMT methylation (+) should receive TMZ alone while those that are (-) should receive radiotherapy alone in hypo fractionated doses.
Patients with recurrent disease should be considered for investigational protocols. Repeat surgical resections could be considered for those where the recurrent tumor is surgically accessible and manifests clinical symptoms via significant mass effect.

Pseudo-progression in Glioblastoma

Reactive changes and tumor necrosis early on (<3 months) post radiotherapy may lead to radiological tumor enlargement i.e. pseudoprogression. An incidence of >20% pseudo-progression has been reported early on post radiochemotherapy (12). Pseudoresponse has been reported with anti angiogenic therapies.
Pseudoprogression has also been reported in patients with solid tumors treated with immunotherapies such as CTLA-4 or avelumab. Early tumor enlargement or even new small distant lesions can be followed later by tumor regression. This could be explained by two possible explanations: immunotherapies require more time to implement tumor control and the initial pseudoprogression is actual progression which later responds; focal inflammatory responses can lead to tissue edema and swelling. The timeframe for immunotherapy induced pseudo-progression remains to be defined but can be present several months post initiation of treatment (37).

GBM induced immunosuppression

The immune surveillance hypothesis was first proposed by Frank MacFarlane in the 1950's. It postulated that the immune system was responsible to detect and destroy tumor cells. This hypothesis has since been modified to encompass three phases; elimination, equilibrium and escape phases of tumor growth. Tumors can avoid initiating an immune response or evade it by numerous mechanisms of which the tumor-induced immune suppression is most relevant to GBM (13).
GBM are known to enact both systemic and local immunosuppressive strategies which enhance tumor progression. They secrete systemic factors which act to decrease T and B-cell responsiveness, cause lymphopenia of CD+4 T cell, and NK cells, while increasing the fraction of Treg cells, reduce immunoglobulin production and influence monocytes to show a decreased antigen presentation and exhibit a myeloid–derived suppressive cell like phenotype (18), (19), (14).

GBM can immunosuppress within its microenvironment creating a perimeter of immune defence by producing cytokines such as transforming growth factor-B (TGF-B), (15) interleukin 2, 6, 10 (IL2,IL6,IL-10) (24, 25) and prostaglandin E (PGE). TGF-B suppresses T-cell proliferation, activation and differentiation into effector cells. GBM produce chemoattractant MCP1 and growth factors which attract microglia and as well chemokines CCL2/22 which attract Treg cells. Indolamine 2, 3 dioxygenase (IDO) is a cytoplasmic enzyme found in GBM cells. It catabolizes tryptophan to kynurenine an immunosuppressive metabolite which can also enhance activation and recruitment of Treg within the tumor microenvironment (26). The microglia which can comprise up to 40% of the tumor mass is induced to express an immunosuppressive M2 phenotype and can produce matrix metalloproteinase 9 and vascular endothelial growth factors (VEGF). They can also secrete IL-10. Both glioma cells and microglia express at their surfaces FAS ligand (FASL) and immune checkpoint regulators such as programmed cell death ligand-1 (PD-L1). These immunosuppressive surface molecules will downregulate the antitumor functions of immune cells such as cytotoxic CD8 T and NK cells by inducing their energy or apoptosis (18, 19).

The majority of tumor infiltrating lymphocytes will express PD1. The reported prevalence of PD-L1 expression on tumor cells varies from 61 to 88% (27) Tumor grade has been correlated with PD-L1 expression and degree of Treg infiltration (21, 22, 23). PD-L1–PD1 interaction suppresses in many ways the local tumor immunoreactivity by reducing T, B and NK cell proliferation, cytokine production such interferon gamma, T cell effector mechanisms such as ADCC and cellular cytotoxicity by CD+8 t cells and NK cells while increasing Treg cells.
Tumor cells can secrete IL-18 which upregulates PD-1 (20).
Anti PD-L1 monoclonal antibody in an animal model of GBM showed an increased survival from 26 to 52 days with a cohort of long term survivors. In the latter group flank re challenge of the tumor did not show any tumor growth which suggest the presence of immune memory.

Immunotherapy
The host's immune response to cancer has been shown to have significant prognostic value (34). Immune infiltrates are heterogeneous between tumour types and between patients for a given tumor. The term immune contexture has been used to represent the host's immune responses to tumor. Some responses such as the expression of an M2 phenotype by macrophages have been clearly demonstrated to favor tumor growth (35.) A strong lymphocytic infiltration especially with CD8+cytotoxic Tells are associated in some cancers with a better survival. Immunotherapy works by improving the immune contexture of tumors. Immunotherapy has been used for decades to fight cancer. Cytokine IL-2, interferons alpha and gamma have been used. More recently immune checkpoint inhibitors anti CTLA-4 (ipilimumab), anti PD-1 (nivolumab and pembrolizumab have received FDA approval for metastatic melanoma and NSCLC (28). The results have been characterized by a relatively delayed and low response rate but with impressive durability suggestive of a possible cure (29). It was also shown that patients who initially had achieved an objective response (>3months) can be successfully retreated once the tumor recurs thus hypothetically re-establishing equilibrium between the immune system and the tumor (29). Tumor PD-L1 expression appears according to recent preliminary data to predict clinical response.

Combination of two immune check point inhibitors such as an anti CTLA-4 targeting the early T-cell activation phase in lymphoid tissue and an anti PD-1 targeting antigen specific T-cells in peripheral tissue and tumors could have a synergistic benefit as suggested in a phase 1 study (29).

Avelumab
Avelumab (company code: MSB0010718C) is a fully human antibody (calculated molecular weight of 143832 Dalton) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1. 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 2 (IL-2) or interferon-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.

The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy appeared to result in an improved anti-tumor activity. In particular, radiation therapy was found to have a synergistic effect when followed by avelumab. The combination has led in somes cases to a complete regression of established tumors presumably through an enhanced anti-tumor immune response and memory (40, 41, 42).

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 which correlated with tumor suppression. Hence, increases in CD8+PD-1+T cells, CD8+ TEM cells, and antigen-specific T cell responses, may be representative of pharmacodynamics (PD) biomarkers with translational relevance to the clinical setting (see product monograph).

The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells
PD-L1 (also called B7-H1 and CD274) 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. 61 to 88% of tumor cells in GBM and the microglia within it express PD-L1
Breaking tolerance by blocking PD-1 interaction with its ligands, and thus PD-1 signaling, can be applied to enhance T cell activity towards chronic pathologies such as cancer

1.2. Rationale

1.2.1. Rationale for Efficacy

A phase 1 trial with 207 patients having a variety of advanced cancer including melanoma, NSCLC, renal-cell cancer, colorectal cancer, pancreatic cancer, ovarian cancer, gastric cancer and breast cancer were treated in an escalating dose ranging from 0.3 to 10mg/kg IV Q2weeks of avelumab. ORR ranged from 6 to 17% and prolonged stabilization of disease ranged from 12 to 41% at 24 weeks. No Maximum Tolerated Dose (MTD) was attained and 9% of patients experienced a grade 3 or higher AE (30).

Ongoing clinical trials with avelumab have shown promising clinical efficacy in a variety of pathologies including non-small cell lung cancer (NSCLC) with ORR of 14%, ovarian cancer with ORR of 8% and gastric cancer with best overall response (BOR) of 15%. Confirmed responses tended to occur between 6 and 18 weeks from onset of treatment with some responding later at 29 weeks from onset.
A phase 1b study where 168 patients with metastatic breast cancer were treated with avelumab 10mg/kg IV Q2weeks with a median follow up of 8 weeks showed an ORR of 4.8% which increased to 33% in patients with >10% of immune cells with the tumor being PD-L1 + (32).

Studies combining ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) and as well studies with pembrolizumab (anti-PD-1) alone in GBM patients are already underway. The nivolumab alone or in combination with ipilimumab in an ongoing study in patients with recurrent GBM has reported a 60% overall survival at 9 months (31). A recent report showed that nivolumab in recurrent high grade glioma is safe when given with concurrent temozolamide and perhaps more effective following repeat radiotherapy.

Avelumab has 2 main mechanisms of action through which it can exert an anti-tumor effect:
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, end the immunotolerance and lead to the 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 (MoAb), 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. Tumor cell lysis via avelumab induced ADCC can be enhanced with concomitant administration of IL-12 or interferon gamma (33).
Therefore, blocking PD-L1 inhibitory mechanisms by interactions with not only PD-1 but also the other ligand, B7-1 and its capacity to induce tumour ADCC, avelumab offers unique therapeutic potential compared with other MoAbs targeting PD-1.

Summary
Patients with GBM despite standard therapy have a dismal prognosis and thus represent a significant unmet medical need. GBM has well documented systemic and local immunosuppressive mechanisms to escape immune surveillance and grow. GBM tumor cells as well as the microglia within it have a high incidence of PD-L1 surface expression which makes it more susceptible to anti-PD-L1 antagonism and ADCC through avelumab therapy. Combination of avelumab with other anticancer therapies have been shown safe and perhaps synergistic. A clinical trial looking at adding avelumab to standard therapy in patients with GBM is therefore indicated.

1.2.2. Rationale for Dose Selection

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.
A concentration of 1 µg/mL of avelumab was required in whole blood to reach a target saturation plateau of >95% target occupancy (TO). Trough serum levels of the drug observed in the dose escalation cohorts in EMR 100070-001, TO would reach or exceed > 95% occupancy throughout the entire dosing interval for 10 out of 13 subjects who received 3 mg/kg, and for all (15/15) subjects who received 10 mg/kg, in the dose escalation group. Thus, it appears that a 10 mg/kg dose of avelumab would achieve

maximal TO in blood in the majority of subjects based on in vitro studies. Using the 1 mg/kg dose, 2 out of 3 subjects displayed less than 90% TO at trough serum concentrations, which were below the quantification limit of 0.2 µg/mL in these 2 subjects.

Therefore, in order to achieve target saturation during the whole treatment period in the majority of subjects, a starting dose of 10 mg/kg of avelumab, intravenous (IV) once every 2 weeks, was selected for the study.

2. CLINICAL SAFETY DATA

As of the safety cut-off 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 maximum tolerated dose (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. 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%), and 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) and infusion-related reaction (each occurred in 9 subjects; 0.7%) followed by lipase increase and fatigue (each occurred in 8 subjects; 0.6%), anemia (7subjects; 0.5%), dyspnea (6 subjects; 0.5%), AST increased (5 subjects; 0.4%), and pneumonitis and autoimmune hepatitis (each occurred in 4 subjects; 0.3%). Other Grade ≥ 3 treatment-related TEAEs that were observed in 3 subjects (0.2%) included asthenia, ALT increased, blood creatine phosphokinase increase, colitis, decreased appetite, hypokalemia, hypoxia, lymphopenia, myositis, transaminases increase, and vomiting. Of the 124 subjects (9.5%) who experienced Grade ≥ 3 treatment-related TEAEs, 99 (7.6%) had Grade 3 events, 21 (1.6%) and 4 (0.3%) reported Grade 4 and Grade 5 treatment-related TEAEs, respectively.

The 21 subjects reporting Grade 4 treatment-related TEAEs experienced events of infusion-related reaction (3 subjects; 0.2%), blood CPK increased, GGT increased, hyperglycemia (2 subjects each; 0.2%), lipase increased, amylase increased, myositis, hypophosphatemia, hypokalemia, embolic stroke, frontal lobe epilepsy, monoplegia, syncope, dyspnea, pneumonitis, respiratory failure, anemia, neutropenia, thrombocytopenia, autoimmune neutropenia, sepsis, cardiac arrest (1 subject each; 0.1%), and 1 uncoded event. The 4 subjects with Grade 5 treatment-related TEAEs

experienced events of radiation pneumonitis, pneumonitis, respiratory distress and acute hepatic failure, autoimmune hepatitis (Grade 3) with consequent fatal liver failure.
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.

Immune-related adverse event (irAEs) are considered AE's of special interest. Treatment-related potential irAEs were observed in 99 of 1300 subjects (7.6%) in the pooled expansion cohort. Hypothyroidism was the most frequent treatment-related potential irAE, which occurred in 45 subjects (3.5%) in the pooled expansion cohort. The other frequent potential irAEs, which were considered as treatment-related, were pneumonitis (13 subjects; 1.0%), hyperthyroidism (7 subjects; 0.5%), adrenal insufficiency and dry eye (5 subjects each; 0.4%), autoimmune hepatitis and colitis (4 subjects each; 0.3%), and myositis (3 subjects; 0.2%). Additional treatment-related potential irAEs were seen in 2 or 1 subjects in the pooled expansion cohort. The majority of potential irAEs were Grade 1 or Grade 2 events. In the pooled expansion cohort, potential irAEs ≥ Grade 3 occurred in 29 (2.2%) subjects. Potential irAEs leading to death occurred in 3 (0.2%) subjects, which were all assessed as treatment-related events. In the pooled expansion cohort, 15 subjects (1.2%) had potential irAEs that led to trial treatment discontinuation. Overall, as of 05 November 2015, there were no treatment-related immune-mediated AEs reported in Trial EMR 100070-001 with onset after the on-treatment period, i.e., 30 days after the last drug administration.

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.

2.1. Immunotherapy Response Assessment in Neuro-Oncology (iRANO)

Previous assessment criteria were done for cytotoxic chemotherapy where the response if it occurs does so within a few weeks of treatment onset and can be measured by tumor shrinkage. Recent studies with immunotherapeutic agents such ipilimumab have shown 4 types of responses: a rapid tumor shrinkage, a prolonged stable disease followed by a slow reduction in tumor burden, an initial increase in tumor size followed by a later sustained shrinkage of the tumor and a shrinkage of the tumor despite the appearance of new lesions. The response also tended to be relatively delayed and may not occur until the post-induction period of therapy. Using the immune-related response criteria (irRC) the ipilimumab melanoma trial would have identified 10% more patients as responders (36).

The Response Assessment for Neuro-Oncology (RANO) criteria were initially proposed in 2010 to improve radiologic assessment of GBM and to encompass pseudo progression and pseudo response phenomenon. A revision for immunotherapy was published in November 2015 (37). It incorporates the irRC and the RANO criteria. The new criteria addresses the issue of initial progressive imaging findings in the context of

patients with neuro-oncological malignancies with a goal of decreasing the likelihood of premature discontinuation of potentially beneficial therapies while ensuring maximum patient safety. The iRANO institutes a 6 months mark whereby radiographic deterioration or new lesions do not constitute progression unless confirmed with a second MRI or CT scan done at least 3 months later. Clinical neurological decline irrespective of imaging findings constitute progression provided the decline cannot be explained by comorbidities or a change in the corticosteroid dose. Radiographic evidence of progression noted after 6 months of instituting immunotherapy is considered tumor progression and do not require confirmation (37) (see section iRANO and appendix 1 for algorithm).

Patients, because the actual duration of pseudoprogression and the time for immunotherapies to become effective are still unknowns will be allowed at the investigator and patient discretion to continue on study treatment during the 3 month period and even after there is confirmation of radiographic or clinical progression unless there is significant drug toxicity.

2.2. Immunoscore

It has become accepted that the host immune contexture has significant value in tumor prognostication and grade. The Immunoscore quantifies two lymphocytes population: CD3/CD45RO and CD3/CD8 within the tumor core and the invasive margin and assigns a score of 0 to 4 with the latter indicative of high density of immune infiltration. This score has been shown in two cohorts of colorectal cancer patients (n=602) to be highly predictive of tumor recurrence and survival at 5 years (38).
In this study using an anti-PD-L1 in patients with GBM the predictive power of the Immunoscore and thus its potential future use as a biomarker in this cancer population will be explored.

3. OBJECTIVES OF THE STUDY

3.1. Primary Objective

To determine the safety and tolerability of avelumab 10mg/kg administered IV Q2weeks in patients receiving standard therapy for newly diagnosed GBM.

3.2. Secondary objectives

To determine the impact of the addition of avelumab in patients receiving standard therapy for newly diagnosed GBM on overall survival, progression free survival and other antitumor activity parameters according to the immunotherapy Response Assessment for Neuro-Oncology (iRANO) at 52 weeks and every 52 weeks thereafter.

3.3. Exploratory objectives

To explore biomarkers that could predict treatment response to avelumab such as: the tumor immunoscore, presence and extent of PD-L1 expression on tumor cells and microglia/macrophages within the tumor

To correlate the OS and PFS to the baseline value and the change from baseline to week 52 and every 52 weeks /or the end of study neurocognitive function as measured by the evoked potential P300 (normal), the baseline corticosteroid dose, the total cumulative corticosteroid dose over the whole study duration, the total cumulative dose of temozolomide since diagnosis and the incidence and severity of irAE's.

To assess and compare above mentioned biomarkers in tissue samples from patients with second surgical resection i.e. treatment failures

To estimate in this GBM population the duration of pseudoprogression and the lagtime needed for immunotherapy to become effective.

4. STUDY DESIGN

4.1. Overview of Study Design

This is a single center, phase 2, open label, open-ended, add-on, single dose study of maximum duration of 260 weeks in patients receiving standard therapy for newly diagnosed GBM. In total 30 patients who meet the entry criteria will be entered into the study within 3 weeks of finishing their last day of combined radiotherapy/temozolomide. Avelumab will be initiated concurrently with the initiation of the first 5 days, monthly cycle of temozolomide.
The study will consist of 3 different phases: Combination Phase a Monotherapy Phase and an Extended Safety Follow-up Phase.

4.2. Treatment Phases of the Study

Combination Phase: Upon completion of the standard combination therapy of radiotherapy (total dose 60 Gy, administered as daily 2Gy fractions, 5 days/week or as per local standard) and temozolomide (75 mg/m2/day p.o. qd) and a treatment break of no more than 21 days, the combination phase will start. Patients will receive temozolomide and avelumab for 6 cycles of 28 days each. During the 1st cycle Temozolomide will be given the first 5 days at a dose of 150mg/m2/day p.o. In the next cycle, the temozolomide dose should be escalated to 200/mg/m2 if permitted by the patient's hematological and non-hematological toxicity profile (as per NCI-CTC AE version 5). The temozolomide dose will be adjusted according to hematological and non-hematological toxicity as per temozolomide's product monograph (appendix 4). Avelumab will be administered on day 1 and day 15 of each cycle at a dose of 10mg/kg IV. Avelumab therapy will be withheld according to the occurrence and severity of avelumab emergent adverse events as per table 3. Patients will continue the

combination of temozolomide (150 – 200mg/m2 per day PO X5 days Q28days) and avelumab (at 10mg/kg dose, IV on days 1 and 15 per cycle) until 6 cycles are completed or until the occurrence of a termination event.

Monotherapy Phase: Upon completion of the Combination Phase or upon stopping temozolomide because of temozolomide related toxicity/tolerability issues or patient choice, the patient will continue into the avelumab Monotherapy Phase. Avelumab 10mg/kg IV Q2weeks will be continued as monotherapy until the occurrence of a termination event defined as one of the following: 1) clinical evidence of neurological deterioration resulting in an ECOG score of at least 3 or more, unexplained by other comorbities, unchanged by an increase in corticosteroid dose and sustained for at least two weeks or 2) treatment emergent adverse event (TEAE) of grade 3 or more or 3) withdrawal of patient consent.

Patients who experience irAE's may according to table 3 directives have their avelumab therapy suspended.

The use of Bevacizumab or re-irradiation will not be allowed in the study and will be considered as evidence of a termination event.

Patients will be promptly informed upon confirmation of disease progression as per the new iRANO criteria. They will be offered to pursue with the avelumab therapy as monotherapy or in combination with other therapies or to withdraw from therapy and enter the Extended Safety Follow up phase. They will need to be reconsented before allowed to continue with the avelumab therapy.

Extended Safety Follow-up Phase:
Patients who discontinue avelumab therapy for any reason at any point in the study will be entered into an extended safety follow-up period of 90 days. New treatment will then be at the investigator or local oncologist's suggestion. All subjects will be observed for the possible occurrence of delayed irAE's for survival data and information about subsequent therapies will be collected. Tissue samples in patients undergoing second surgical resections will be obtained for further biomarker analysis.

4.3. Treatment Allocation

This is an open label, open- ended, single center add-on study

4.4. Number of Subjects

A total of 30 patients will be recruited.

4.5. Centers

This is a single center investigator initiated study.

5. ENDPOINTS

5.1. Primary

Safety and tolerability based on avelumab treatment emergent adverse events leading to permanent or transient discontinuation of avelumab
Treatment emergent adverse events of special interest will include those of autoimmune origin (irAE).
The adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

5.2. Secondary

Radiological tumor response will be graded according to the Immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria by a single study radiologist based on the gadolinium enhanced brain MRI or CT scan performed at the study center at baseline and Q52weeks or within 2 weeks of an end of study visit and evaluations of locally obtained MRI's or CT scan.
Clinical tumor response as per the iRANO criteria will be evaluated by the principal investigator based on the protocol specified neurological exams
The iRANO endpoints will be stratified in relation to MGMT status, baseline age (>50yrs), baseline Karnofsky performance score (score of 100), radical tumor resection vs biopsy, primary versus secondary GBM.

Changes in the daily corticosteroid dose will be discouraged during the 2 weeks period prior to the week 52 or end of study visit MRI or CT scan.

iRANO:

During the study

Progression of Disease (PD) based on clinical parameters:
Patients at any time with significant, clinical neurological deterioration resulting in an ECOG score of 3 or more, sustained for more than 2 weeks, unchanged by an increase in steroids or unexplained by concurrent comorbidity will be considered as having progressed and confirmatory imaging will not be required.
The SPD is the sum of the products of biperpendicular diameters of the measurable enhancing lesions (max 5 lesions).

Progression of Disease (PD) based on radiographic parameters:
Patients with stable clinical neurological status with stable dexamethasone dose of 12mg/day or less and evidence of radiological progression defined as a ≥25% increase in the sum of the biperpendicular diameters of enhancing disease~~,~~ or substantial worsened T2/FLAIR;or new lesions on gadolinium enhanced MRI or CT scan done less than 6 months from baseline will require confirmation on a repeat imaging done 3 months later. The first MRI or CT scan showing progression will act as the new baseline and if progression is confirmed the date of progression will be backdated to the new baseline MRI or CT scan where the progression was first noted.
If the first radiological evidence of progression or new lesions occurs 6 months or more from baseline then no confirmatory imaging will be required.

At week 260 or end of study visit

Progression of Disease (PD) will be defined as a ≥25% increase on the 12 month MRI in the sum of the product of the biperpendicular diameters of enhancing disease; or new lesions; or substantial worsened T2/FLAIR; or significant clinical neurological decline unexplained by a change in medication or concurrent comorbities. The SPD is the sum of the products of biperpendicular diameters of the measurable enhancing lesions (max 5 lesions)

Complete Response (CR) will be defined as the disappearance on the month 12 MRI or CT scan of all enhancing disease, no new lesions, with stable or improved T2/FLAIR; no more than physiological steroids; clinically stable or improved

Partial Response (PR) will be defined as a ≥50% decrease on the month 12 MRI or CT scan in the sum of the products of the biperpendicular diameters of enhancing disease, no new lesions, stable or improved T2/FLAIR, stable (>2 months) or decreased steroid dose, clinically stable or improved

Stable Disease (SD) will be defined as a patient who do not qualify for complete response, partial response, or progressive disease, stable or improved T2/FLAIR; stable (>2 months) or decreased steroid dose, clinically stable or improved

Overall survival (OS) will be defined as the time from baseline to the date of death from any cause. Follow up times of patients who are lost to follow up will be recorded and censored. The censoring time point (date last known to be alive) will be recorded.

Objective Response Rate (ORR) will be defined as the number of patients with CR + PR - divided by the total number of patients at time points 12, and every 12 months thereafter.

Progression Free Survival (PFS) will be defined as the time from baseline to documented PD or death from any cause. Patients without event would be censored at the last valid tumor assessment (before starting new anti-cancer therapy) at which they were known to be progression-free.

5.3. Exploratory

The correlation between OS and PFS and the prevalence of PD-L1 expression on tumor cells and microglia/macrophages within the tumor, the histological immunoscore.
The correlation between OS and PFS and the baseline corticosteroid dose, the total cumulative corticosteroid dose over the whole study duration, the total cumulative dose of temozolomide since diagnosis, the baseline value and the change from baseline to week 52 visit and/or the end of study neurocognitive function as measured by the evoked potential P300 and the incidence and severity of irAE's.

The change between baseline biomarker results and those obtained from biomarkers in tissue samples from patients with second surgical resection i.e. treatment failures

The description of the time period in which radiological progression was seen in clinically stable patients whose imaging was subsequently followed by radiological stabilization or regression
The description of the time period in clinically stable patients before radiological evidence tumor regression occurred
The change in P300 evoked potential values and its correlation with clinical outcomes

Safety monitoring: There will be an internal DSMB which will make annual reviews.

6. END OF STUDY

6.1. Definition of End of Study

This is an event driven trial. The end of the trial will be when the last data of the last patient required for the overall survival analysis has been received. Complete analysis will be done when all patients have completed week 52 or end of study visit and then every 52 weeks thereafter.
The study may also be prematurely terminated by the sponsor.

6.2. Criteria for Premature Withdrawal

Withdrawal from the study treatment /study
The investigator can/must discontinue study treatment for a patient in the event of:

- Progressive disease (as per iRANO)
- Intercurrent illness
- Unacceptable toxicity (grade 3 or higher)
- Protocol violation
- Pregnancy
- Patient request
- In the case that the patient decides to prematurely discontinue study treatment he/she will be offered to continue into the Extended Safety Follow-up Phase
- In the case the patient decides not to or is unable to continue into the extended follow up phase then he/she will be withdrawn from the study. He /she will with the patient's permission be followed for survival assessment with monthly

telephone calls. Otherwise the patient will be considered lost to follow-up. The outcome of these discussions should be documented in both the medical records and in the CRF.

- Similarly, the investigator has the right to withdraw patients from the study in the event of intercurrent illness, unacceptable toxicity, protocol violation, pregnancy and administrative or other reasons. Patients have the right to withdraw from the study at any time for any reason.
- An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

7. STUDY POPULATION

Patients with newly diagnosed glioblastoma histologically confirmed with surgical resection or biopsy, who will be undergoing or have finished the standard temozolomide/radiotherapy no more than 3 weeks ago.

7.1. Inclusion criteria

1. Signed informed consent
2. Age ≥ 18 years
3. Present with newly diagnosed supratentorial Glioblastoma (GBM) with a tissue diagnosis that has been established following either a surgical resection or biopsy. This includes treatment-naïve - (chemotherapy and radiotherapy)- patients with prior diagnosis of a lower grade astrocytoma that has been upgraded to a histologically verified GBM
4. Karnofsky performance score of 70 or higher
5. Patients entering the study must be on a stable dose of no more than 12 mg (maximum) of Dexamethasone (or equivalent) daily for symptoms related to cerebral edema
6. Will be or is undergoing or has received the standard therapy of chemo radiation therapy (60Gy in 30 fractions of 2Gy/day or as per local protocol with concurrent temozolomide of 75mg/m^2 per day PO or as per local practise) no more than 21 days ago
7. Has not yet begun but will begin standard monthly temozolomide therapy
8. Patient must have at least 1 formalin fixed paraffin embedded tumor tissue block representative of glioblastoma available for biomarker analysis and determination of MGMT status (if not already done). If tumor block is not available or not of adequate quality, sufficient pathology material, representative of glioblastoma, must be available
9. Adequate hematological function defined by absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused)
10. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤ 2.5 × ULN for all subjects

11. Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
12. Negative serum pregnancy test at screening for women of childbearing potential
13. Highly effective contraception for both male and female subjects if the risk of conception exists. (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required at least 28 days prior, throughout and for at least 30 days after avelumab treatment.
14. International normalized ratio (INR) or PT (secs) and activated partial thromboplastin time (aPTT):
    – in the absence of therapeutic intent to anticoagulate the subject:
    INR≤1.5 or PT ≤1.5 x ULN and aPTT ≤1.5 x ULN
    – in the presence of therapeutic intent to anticoagulate the subject:
    INR or PT and aPTT within therapeutic limits (according to the medical standard in the institution)
    NOTE: Use of full-dose anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to baseline.
15. Willing and able to comply with the protocol as judged by the Investigator

7.2. Exclusion Criteria

1. Patients who have evidence of leptomeningeal disease
2. Known significant pulmonary, cardiovascular, hepatic disorders or any other disease that in the opinion of the investigator would be contraindicated to receive anti PD-L1 therapy such as avelumab,
3. "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 (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication."

4. Prior treatment with bevacizumab or any checkpoint immune blockade therapies
5. Any other concomitant immunosuppressant other than temozolomide and steroids or any recent (within 3 months) experimental therapy
6. Patients who have finished their radiotherapy course more than 3 weeks prior to baseline
7. Prior organ transplantation, including allogeneic stem-cell transplantation
8. Significant acute or chronic infections including, among others:
   - Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS),

- Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive),

9. Active autoimmune disease that require ongoing corticosteroid and/or immunosuppressant therapy that might deteriorate when receiving an immunostimulatory agent:

    - Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease or any other autoimmune disease not requiring immunosuppressive treatment are at the investigator's discretion eligible
    - Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day
    - Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable

10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)
11. Pregnancy or lactation
12. Known alcohol or drug abuse
13. Any psychiatric or cognitive condition that would prohibit the understanding or rendering of informed consent
14. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines
15. Any other malignancy within 5 years prior to baseline, except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix
16. Evidence of any active infection requiring hospitalization or IV antibiotics within 2 weeks prior to baseline.
17. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
18. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, 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.

8. CONCOMITANT MEDICATION AND TREATMENT

8.1. Concomitant medication

All concomitant medication(s), including over the counter drugs, blood products etc., administered to patients from baseline up until the safety follow-up visit must be reported in the Case Report Form (CRF).

Corticosteroids administered to the patient for disease control must be reported in the CRF. Dosage, frequency, dates of administration, and route of administration must be recorded in the dedicated CRF pages.
Any diagnostic, therapeutic or surgical procedure performed during the study treatment period must be recorded with corresponding dates, description and any clinical findings.

8.2. Not permitted concomitant treatment

The following treatments are **NOT** permitted:
- Bevacizumab or re-irradiation will not be allowed in the treatment phases of the study and will be considered as evidence of disease progression.

– Treatment with other systemic anti-cancer agents before disease progression has been confirmed (chemotherapy, hormonal therapy, immunotherapy, vaccines, targeted agents, retinoic acids, or other treatments not part of protocol-specified anti-cancer therapy)
– Concurrent investigational agents of any type before disease progression has been confirmed
– Any medications contraindicated with the chemotherapy regimen (temozolomide) are not permitted and special warnings and precautions for the use of temozolomide should be observed (as long as the patient receives temozolomide)
–Intra-tumoral interstitial therapy, or any form of radiosurgery
Any of the above will lead to patient's discontinuation from study treatment.

8.3. Anticoagulation

Use of full-dose anticoagulants is permitted as long as at the time of baseline the INR (or PT [secs]) and aPTT are within therapeutic limits (according to the medical standard in the institution) AND the patient has been on a stable dose of anticoagulants for at least two weeks.
During the study, the preferred choice for anticoagulation treatment with therapeutic intent should be low molecular weight heparin as per ASCO guidelines In this case, levels of anti-Xa should be within the therapeutic range.
Caution should however, always be exercised, patients adequately supervised, and all anti-coagulant medications recorded in the appropriate CRF page.
If a patient suffers a thromboembolic event, it may be possible for him/her to remain on study treatment.

8.4. Supportive care guidelines

– Supportive care therapy (e.g. antiemetic, antidiarrheal, hydration, etc.) should be prescribed according to local practice.

– Use of colony-stimulating factors (e.g., G-CSF, GM-CSF, erythropoietin, etc.) in a manner consistent with product labeling is discouraged but permitted at the discretion of the Investigator or treating oncologist. However, G-CSF and other colony stimulating factors should not be administered to allow temozolomide administration at a higher dose or to avoid temozolomide interruption during the radiotherapy.

– The duration of treatment with the maximum dose of 12 mg should be no more than 7 consecutive days. The investigator(s) should make every effort to taper the Dexamethasone as soon as symptom improvement allows to the lowest tolerable dose that controls the CNS symptoms. Corticosteroid use for iAE's will be done according to the treatment algorithms in the appendix. The use of other immunosuppressant such as rituximab, etc. will not be allowed and will lead to study withdrawal due to study drug immune related adverse event (iAE).
Changes in corticosteroid dosage will be discouraged in the period 2 weeks prior to the 12 months MRI or CT scan.
Patients who for control of peritumoral edema require doses of dexamethasone greater than 12mg/day or its equivalent or for periods longer than 7 days will be considered as having disease progression unless this occurs within the first 3 months of the study.

Bevacizumab or re-irradiation will not be allowed in the study.
Antiepileptic therapy will be allowed if required. The choice of antiepileptic agent will be according to best medical fit for each patient. Hepatic enzyme inducers should however be avoided.

Upon confirmation of disease progression as per the new iRANO criteria, (see section) patients will be treated at the investigator or local oncologist's discretion. Patients who have confirmed radiological progression without evidence of study drug toxicity will at the investigator and patient's discretion be allowed to continue with study drug. All subjects will be followed for survival data collection and information about subsequent therapies will be collected. Tissue samples in patients undergoing second surgical resections will be obtained for further biomarker analysis.

9. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The type of assessments to be performed and their timing in the respective study periods are summarized in Table 1

9.1. Screening Examination and Eligibility Screening Form

All patients will provide written informed consent (IC) before any study specific procedure is performed.
An eligibility screening form (ESF) documenting the patient's fulfillment of the entry criteria, must be completed by the investigator/designee for all patients considered for the study and subsequently included or excluded from participation. Patients who are considered for study entry, but fail to meet the eligibility requirements, should also have an ESF completed with the non-eligibility reason given (it provides information on the selected trial population). This information will not be entered on the clinical trial database but will be collected with the reason for screen failure. All ESFs should be kept in the study files at the sites.
A CRF will only be completed for patients fulfilling the entry criteria.

9.2. Procedures for Enrolment of Eligible Subjects

Once a subject has fulfilled the entry criteria a subject Enrolment and Identification Code will be attributed and inscribed in the Enrolment and Identification Code List. The latter must be maintained by the investigator.
Baseline evaluation and start of treatment should occur on the same day. When this is not feasible, the delay between baseline evaluation and start of treatment must be kept to a minimum and should not exceed 7 days.

9.3. Clinical Assessments and Procedures

9.3.1. **Screening and Baseline Procedures**

All screening and baseline study related activities are summarized in table1. All patients should provide written informed consent before any study specific procedures are performed.

9.3.1.1. Screening Assessments

Must occur between weeks -12 and -1 of the baseline visit
Demographics and medical history, which include:
– previous and current diseases
– history of glioblastoma, including date of diagnosis, history of prior low grade astrocytoma, location of disease, details of surgery performed
– all medication and surgeries over the last 1 month prior to inclusion into the study (including all over the counter and herbal remedies).
– neurological examination
- signs and symptoms related to GBM
- a complete physical examination, which includes vital signs (sitting blood pressure and body temperature), physical measurements (body weight and height)
- hematology, blood chemistry and urine analysis, a urine dipstick test, coagulation parameters within weeks -2 and week -1 of the baseline visit
- a serum β-HCG test should be performed for all women with an intact uterus (unless amenorrhoeic for the last 24 months).
- the Karnofsky performance score (KPS) within 2 weeks of the baseline visit.
- a P300 evoked potential within 2 weeks of baseline visit
- a study specific gadolinium enhanced MRI or CT scan within 2 weeks of baseline visit
- the corticosteroid dosage must be noted

NOTE: In case of a delay of the first dose of study treatment, then any assessments required to meet study entry criteria (P300 and MRI or CT scan expected) have to be repeated if more than 2 weeks have elapsed.

9.3.1.2. **Assessments at Baseline**

The baseline visit and the start of treatment will occur on the same day. If not possible then a delay of no more than 7 days will occur between the two.

Assessments will be as specified in the schedule of visits in table 1
Once the study entrance criteria are reconfirmed patients will receive their first dose of the avelumab.
Vital signs and a pre infusion questionnaire will be done with the infusion nurse prior to starting infusion.
Patients will receive the first dose of the five day course of temozolomide according to standard therapy that same evening and for the subsequent 4 evenings.

9.3.2. Assessments during the Combination and the Monotherapy Phases

A history, physical and neurological exam will be performed by a physician every 4weeks before the avelumab infusion to determine if there is evidence of toxicity or tumor progression every 4 weeks for the first 12 weeks and then every 12 weeks or at the end of treatment and 30 days after.

A pre-infusion questionnaire and vital signs will be done by the nurse prior to each infusion (ieQ2weeks). If these suggest evidence of significant toxicity or tumor progression then the patient will be referred to the physician for evaluation.
Laboratory evaluations will be done prior to each infusion (i.e. Q2weeks) at the end of treatment and 30 days after to look for evidence of toxicity.
Non-study specified MRI or CT scan done for safety evaluations will be performed according to local standard practise usually Q3-4 months.

Note: An unscheduled disease assessment may be performed at the discretion of the investigator or at the request of the infusion nurse to ascertain if there is significant toxicity or clinical evidence of tumor progression
All AE's will be graded according to the NCI-CTC AE, version 5.0

9.3.3 Assessments during the Extended Safety Follow-up Phase:

Patients will undergo a physical and neurological exam as well as hematological and blood chemistry and thyroid evaluations at day 30 post end of treatment and telephone follow-up calls monthly x2
Pathology samples will be obtained for repeat biomarker analysis if a second tumor surgery occurs

9.3.4. Assessments at end of study

An end of treatment study visit will occur when:

1) Grade 3 or higher avelumab related toxicity occurs
2) Evidence as per the iRANO criteria of tumor progression occurs and patient does not wish to continue treatment
3) Patient wishes for any reason to discontinue treatment or withdraw from the study. Clinical evidence of neurological deterioration resulting in an ECOG score

of at least 3 or more, unexplained by other comorbities, unchanged by an increase in corticosteroid dose and sustained for at least two weeks.

A history, physical and neurological exam will be performed by a physician. Laboratory test as per schedule will be drawn. If any of the latter have already been performed to confirm the AE or tumor progression on the basis clinical neurological deterioration, then they need not be repeated.

A study specified gadolinium enhanced MRI or CT scan will be performed within 2 weeks of the end of study visit for all patients after 52 weeks.
Patients however who discontinue the study treatment on the basis of avelumab treatment related AE's or clinical evidence of tumor progression a study specified MRI or CT scan will be done at the discretion of the investigator.

Patients who prematurely discontinue study treatment will be encouraged to continue into the Extended Safety Follow-up phase of the study
Patients who not only end treatment but also withdraw from the study, for any reason, will be encouraged to have telephone follow ups every month in order to obtain survival information with regards to OS. Pathology samples will be obtained for repeat biomarker analysis if a second tumor surgery occurs

NOTE: Since the actual duration of pseudoprogression and the time for immunotherapies to become effective in patients with GBM are still unknowns patients will be allowed at the investigator and patient discretion to continue on study treatment after confirmation of radiographic progression unless there is significant drug toxicity Grade 3 or higher AE's unrelated to avelumab such as those secondary to intercurrent illness or temozolomide therapy do not constitute for the purpose of this study a reason to withhold avelumab therapy or withdraw the patient from the study.

9.3.5. **Disease assessment Evaluation**

Disease assessment evaluations will be based according to the immunotherapy Response Assessment for Neuro-Oncology (iRANO).

Study specified MRI's or CT scan will be done at the baseline, week 52 and every 52 weeks. These will be performed at a single MRI center using a predefined acquisition protocol (appendix 3). Change in the corticosteroid dose within the 2 week period preceding the week 52 MRI or CT scan will be discouraged.

All other MRI's or CT scan performed mainly for safety reasons will be done locally according to standard practise usually every 3 to 4 months. Copies of these MRI's or CT scan will be obtained for review by the investigator. These will also be used after the 6 month mark to ascertain if there is radiological evidence of progression according to the iRANO criteria (see page 29).

It is strongly encouraged that for a given patient the same physician will do the physical and neurological evaluations to confirm AE's or tumor progression during the entire study

Neurological Examination:
Evaluation of neurological function at each disease assessment will be based purely on the investigator's assessment of the patient's neurological state compared to the neurological function at the time of the last assessment visit. Neurological function must be recorded as Improved, Unchanged, or Worsened.
In the absence of progression based on radiological assessment, patients who clearly neurologically worsen compared to neurological evaluation at the last disease assessment, and whose corticosteroids use is unchanged or increased compared to the previous disease assessment, will be considered to have evidence of disease progression.

NOTE: Neurological deterioration independent from the disease being treated should not be considered in the context of the Disease Assessments.

Corticosteroids use: at the time of each disease assessment the corticosteroid intake will be compared to corticosteroid intake at the time of the last disease assessment. The changes and dose will be recorded as Increased, Unchanged or Decreased. Increases and decreases in corticosteroid intake should be clinically justified.

NOTE: Increases in corticosteroid dose for reasons other than for tumor disease control especially if done to control immune related AE's need to be recorded and taken into consideration when making this comparison.
The corticosteroid dose should be kept stable for 14 days prior to the 12 months MRI or CT scan in order to minimize interference of corticosteroids in the interpretation of response.

Radiological assessment: patients who have undergone gross total resection and show neither contrast-enhancing (index lesions) nor non-enhancing lesions (non- index lesions) on MRI or CT scan will be followed for recurrence (the appearance of one or more new lesions). If no signs of progression are observed on the MRI or CT scan, then these patients should have a radiological assessment recorded as "No Change". However, in case of unequivocal evidence of progressive disease (major deterioration in neurological function, and unchanged or increased corticosteroid dose) the Overall Disease Assessment will be "progressive disease". Progressive disease will not need a confirmatory scan.
For index lesions the Sum of the Product of the biperpendicular Diameters of the measurable enhancing lesions (SPD) will be recorded and used for comparison. An increase in the lesion SPD noted prior to month 6 will require confirmation 3 months later using the last MRI or CT scan as baseline comparison. The 12 months MRI or CT scan will be compared to baseline.

Performance status
Performance Status (PS) will be measured using the Karnofsky performance status scale (Appendix 2).

9.3.6. Safety assessment

The NCI CTC-AE version 5.0 will be used to evaluate the clinical safety of the treatment in this study. Patients will be assessed for adverse events at each clinical visit and as necessary throughout the study.

Safety Laboratory Assessments
The following laboratory parameters will be used for patient safety:

Hematology
• Hemoglobin, platelet count, WBC count, absolute neutrophils and lymphocytes

Coagulation Tests
• INR, and aPTT

Blood chemistry
• Including total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, phosphate, serum creatinine, and electrolytes (sodium, potassium, calcium), glucose, amylase, lipase, TSH, GGT, CK

Urinalysis
• A urine dipstick test

Pregnancy test
• Serum β-HCG test indicated in pre-menopausal women who are not surgically sterile and women < 2 years after the onset of menopause

Additional tests may be done at the discretion of the investigator for patient safety.

9.3.7. Follow-up

All patients who discontinue from study treatment will be followed for survival information.
In addition, patients who withdraw from study treatment as a result of progressive disease all further anti-neoplastic treatment, (including surgery and re-irradiation) will be recorded until death or end of the study whichever occurs first.
Survival telephone visits will be performed every 4 weeks until death or the end of the study, whichever occurs first.

For patients who prematurely withdraw from study treatment without documented disease progression:

Disease assessments will be performed until disease progression is observed. All further anti-neoplastic treatment (including surgery and re-irradiation) will be recorded until death or end of the study whichever occurs first. Telephone survival visits will be performed every 4 weeks until death or the end of the study, whichever occurs first.

If the patient withdraws consent, this request must be documented in the source documents, and signed by the investigator. At this time, the patient will be asked if he/she agrees to be followed-up for collection of survival information. This agreement must be documented and signed by the investigator. The study staff may also use a public information source to obtain information about survival status.

9.3.8. Other assessments

Immunoscore and PD-L1 analyses and MGMT Status Assessment
A local pathology report will constitute adequate documentation of histology for study inclusion; however, the tumor block used for diagnosis of GBM must be collected for each patient and sent for biomarker analyses, immunoscore determination and MGMT assessment (if not already done). The availability of these samples is mandatory for participation into the study, and they must be sent within 2 months after patient's entering the study.
Paraffin embedded blocks containing formalin-fixed tumor tissue representative of the glioblastoma diagnosis is the preferred sample if available, and of sufficient quality), otherwise, a partial tumor block, or pathology material should be sent If surgery was not performed but biopsy was performed (or if it is not possible to send FFPE tumor tissue blocks) **at least 10 unstained, uncovered slides** must be sent.

Neurocognitive Function
Baseline neurocognitive function has been shown to have prognostic value in patients with GBM. The P300 evoked potential is an electrophysiological measure of a person's capacity to assign attention to a specific stimulus. The measure has shown good correlation (ICC of 0.7) with cognitive status in neurodegenerative diseases. It is a painless, easy measure to obtain. We hope that it will circumvent some of the shortcomings of using neuropsychological scales in assessing the overall general neurocognitive status of patients.
The P300 will be performed at baseline, every 52 weeks and at end of study visit (week 260 or at PD)

Table 1: STUDY ACTIVITIES

Tests and Evaluations	Screening Visit	Combination/ phase Week 0 to 24 Visit window: ±2 days													Monotherapy phase Week 26 to 52 [4] Visit window: ±2 days																Extended safety follow-up phase[1,2]
Week	**-12 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**EOS**	
Informed Consent	X																													
Demographics Medical History	X																													
Physical Exam	X	X		X		X		X						X						X						X			X	X
Neurological Exam	X	X		X		X		X						X						X						X			X	X
Karnofsky	X	X																												
Vital Sign	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lab's[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MRI or CT scan		X																										X	X	
P300		X																										X	X	
AE's and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-infusion questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Avelumab infusion Q 2 weeks		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Temozolomide		X		X		X		X		X		X		X																

See foot note on the next page

1 The Extended Safety phase will involve a site visit at day 30 and telephone follow-up at day 60 and 90 post end of treatment. A second site visit may be required if there is any concern

2. Patients who withdraw prematurely from the treatment or complete the 260 weeks of treatment will be offered to enter the Extended safety follow-up phase

3.Lab's: **Hematology** will include Hemoglobin, platelet count, WBC count, absolute neutrophils, and lymphocytes. **Coagulation** will include INR, and aPTT **(at screening or baseline only)**. **Blood chemistry** will include total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, phosphate, serum creatinine, and electrolytes (sodium, potassium, calcium), glucose, amylase, lipase, TSH, GGT, CK. **Urinalysis** will include urine dipstick test. **Serum β-HCG** must be performed at screening in women of childbearing potential. Subsequent **urine β-HCG** must be collected monthly. Additional tests may be done at the discretion of the investigator for patient safety.

TSH T4 will be collected Q8weeks and repeated at the Extended Safety visit

4. study visit will continue Q2weeks until the occurrence of a termination event.

Survival telephone visits will be performed every 4 weeks until death or the end of the study, whichever occurs first

10. INVESTIGATIONAL MEDICINAL PRODUCT

10.1. Dose and Schedule of Test Drug

Avelumab is a fully human IgG1 antibody directed against PD-L1. 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.

Avelumab will be administered intravenously every 14 days starting the same day as the first day of the first 5 days po temozolomide treatment. Temozolomide's 28 days cycle will be repeated 6 times or until grade 3 or higher temozolomide related treatment AE's. Avelumab will be continued IV q14 days for 260 weeks or until grade 3 or higher avelumab treatment-related AE's occurs and independent of whether the patient continues or completes the 6 cycles of temozolomide.
Avelumab may be withheld temporarily in the case of irAE according to the irAE's algorythms (table 3)
Temozolomide dose may be adjusted or withheld according to the directives in the temozolomide's product monograph (appendix 4)

10.2. Avelumab

Avelumab drug product is a sterile, clear, and colorless 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). For avelumab drug product, only excipients that conform to the current Ph. Eur. and/or the current USP are used.

Instructions for Avelumab Administration and 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.

For administration in clinical trials, 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 if needed. 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.

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

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.
To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel:
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. For detailed information on the assigned dose levels and the concrete volumes to be replaced to prepare the target doses, please refer to the clinical trial protocol or to the manual of preparation.

10.3. Temozolomide

Institutions should follow their standard guidelines for temozolomide. Temozolomide is taken orally on a daily basis during the chemoradiotherapy (75 mg/m2 p.o.) and for the first 5 days of each cycle during the six cycles of the Combination Phase with a starting dose of 150 mg/m2 po qd which in the absence of tolerability or toxicity issues may be escalated to 200mg/m2 po qd in the second or subsequent cycles.

10.4. Radiotherapy

Patients will have received standard total of 60Gy in 2 Gy daily fractions 5 days a week for 6 weeks

11. SAFETY ASSESSMENT

11.1. Adverse Event (AE) and AE Reporting

11.1.1. Definition of a Clinical Adverse Events

Per the International Conference of Harmonization (ICH) an AE is any unfavorable and unintended medical occurrence/sign (including an abnormal laboratory finding), symptom or disease in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions which worsen during a study are also to be reported as AEs.
Each AE term is mapped to a MedDRA preferred term.

11.1.2. Reporting and Grading of an Adverse Event

Adverse events will be reported and graded following National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE). Accordingly, intensity of all adverse events will be graded on a five-point scale (Grade 1 to 5) and reported in detail on the CRF. Reporting of AE based on CTCAE terms and corresponding grading are an integral part of safety/AE/SAE reporting in this study and will have to be strictly followed. Adverse events not listed on the CTCAE should be graded as instructed in table 3.

11.1.3. Causal Relationship between 'Treatment' and the Adverse Event

The causality relationship of study 'treatment' to the adverse event will be assessed by the investigator as either: **Yes or No or probably**
If there is a reasonable suspected causal relationship to the study treatment, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.
The investigator should provide his/her assessment as to whether an AE is related to each individual component of the study treatment regimen (i.e. temozolomide and/or avelumab).
The following criteria should be considered in order to assess the relationship as **Yes:**
• Reasonable temporal association with drug administration
• It may or may not have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
• Known response pattern to suspected drug
• Disappears or decreases on cessation or reduction in dose
• Reappears on rechallenge.
The following criteria should be considered in order to assess the relationship as **No**:
• It does not follow a reasonable temporal sequence from administration of the drug.
• It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
• It does not follow a known pattern of response to the suspected drug.
• It does not reappear or worsen when the drug is re-administered.

11.2. Serious Adverse Event

A serious adverse event is any adverse event that fulfils at least one of the following criteria:
• is fatal; (results in death; NOTE: death is an outcome, not an event)

• is Life-Threatening (NOTE: the term "Life-Threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
• requires in-patient hospitalization or prolongation of existing hospitalization;
• results in persistent or significant disability/incapacity;
• is a congenital anomaly/birth defect;
• is medically significant or requires intervention to prevent one or other of the outcomes listed above
All AEs that do not meet any of the criteria for seriousness should be regarded **as nonserious AEs**.

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of a specific AE, e.g., mild (Grade1), moderate (Grade 2), or severe (Grade 3) myocardial infarction. “Serious” is a regulatory definition (see previous definition) and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities. Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.
The study will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting**

11.3. Adverse Events of Special Interest

Adverse events of special interest will include those of autoimmune origin (iAE).

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur.

11.4. Treatment Emergent Adverse Event (TEAE) Requiring Avelumab Discontinuation or Modifications

The following TEAE’s require permanent treatment discontinuation of avelumab:

- **Any Grade 4 TEAE require treatment discontinuation with avelumab** except for 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

- **Any Grade 3 TEAE’s require treatment discontinuation with avelumab except for any of the following:**
  - Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
  - Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1

- Single laboratory values out of normal range (excluding Grade ≥ 3 AST or ALT combined with ≥2 ULN total bilirubin) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of Avelumab administration)

- **Any Grade 2 TEAE should be managed as follows:**

If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.

- If a Grade 2 TEAE does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with avelumab. TEAE (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 TEAE (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.
- Infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), and tumor lysis syndrome should be handled according to guidelines provided.

The Management for Symptoms of Infusion-Related Reactions are listed in the table below:

Table 2: Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 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.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study avelumab and must not receive any further avelumab treatment.
- 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. - If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

11.5. Severe Hypersensitivity Reactions and Flu-Like Symptoms

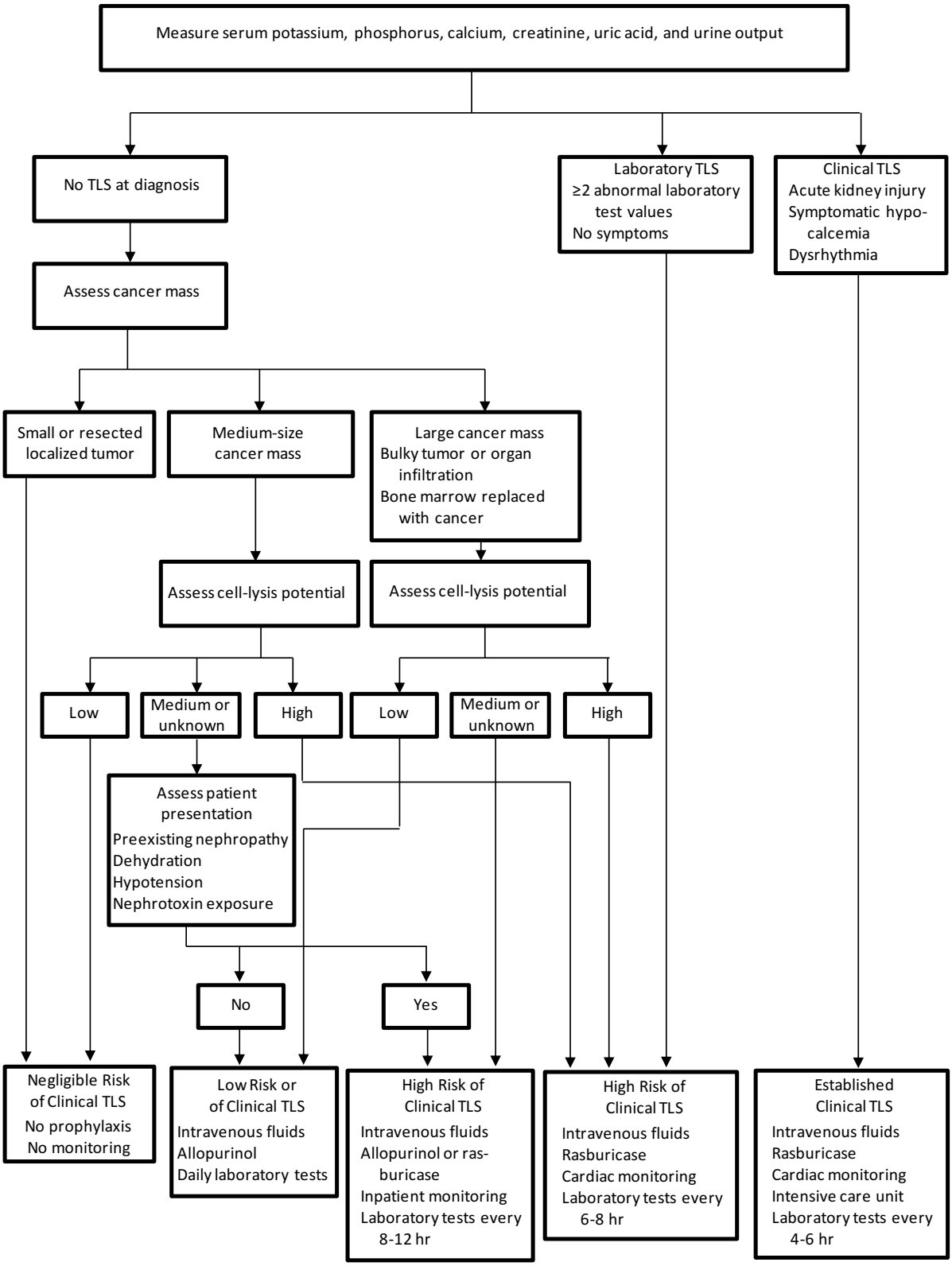
If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

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.

Tumor Lysis Syndrome

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity, there is a theorical risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm below (Howard, Jones, & Pui 2011) (39). TLS has not been seen with avelumab.

Assessment and Initial Management of Tumor Lysis Syndrome



11.6. Immune related Adverse Event (irAE)

Immune checkpoint inhibitors are known to cause autoimmune adverse events. Previous studies with avelumab has shown an incidence of 9.7% most of them of grade 2 severity.
Any untoward medical occurrence, sign/symptom, disease, including laboratory abnormality or exacerbation of previous condition occurring during the study drug and believed to be of autoimmune origin will be classified as an immune related/emergent autoimmune adverse event (irAE).

Treatment of irAE's is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, 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 irAEs should follow guidelines set forth in the table below (table 3).

Table 3: Management of Immune-mediated Adverse Reactions

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade): Grade 1 to 2: treat symptomatically or with moderate dose steroids, 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 the table below Table 4.		
Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4

Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5 to 7 days or recur: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	withhold avelumab for Grade 3 Permanently discontinue avelumab for Grade 4 or recuurent Grade 3 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	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 > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If Grade 2 persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisone IV 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
Grade 3 to 4 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	If improves to Grade ≤ 1: Taper steroids over at least 1 month, resume avelumab therapy following steroids taper (for initial Grade 3).

	1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 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
Grade 2 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 prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: life-threatening	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	If improves to Grade ≤ 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)

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤1: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsens: Treat as Grade 3 to 4
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalentAdd prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 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

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 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.

Grade 2 to 3 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.
Grade 4 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	**Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg. troponin, CK-muscle/brain, 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-related myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-related etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-related myocarditis.
Immune-related myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (eg. azathioprine, cyclosporine A)

	Add prophylactic antibiotics for opportunistic infections.	
*Local guidelines, or eg. *European Society of Cardiology* or *American Heart Association* guidelines *European Society of Cardiology*E guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines *American Heart Association* guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed 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. Rule-out secondary endocrinopathies (ie. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult 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. Rule-out secondary endocrinopathies (ie. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie. subnormal serum thyroxine with inappropriately low thyroid-stimulating	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).

	hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone)) : • 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) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • 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. • Add prophylactic antibiotics for opportunistic infections.	In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	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.

Grade 2 irAE or first occurrence of Grade 3 irAE	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.
Recurrence of same Grade 3 irAEs	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	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	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.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
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 **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine 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.

11.7 Infusion related Reactions

Symptoms related to infusions are listed below:

- Fever
- Chills
- Rigors
- Diaphoresis
- Headache

11.8. Assessments of all events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 11.2.
- The relationship of the event to study procedures as defined in Section 11.11.1.
- The severity of the event as defined in Section 11.11.2.

11.9. Immediate Reporting of Serious Adverse Events

The Sponsor-Investigator primary responsibilities for safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and EMD Serono, as required by local regulations (for regulatory reporting) and as required by the ISS agreement (for reporting to EMD Serono).

The following reportable events must be submitted to EMD Serono within 24 hours (or immediately for death or life-threatening events) using the applicable safety report form provided. [The Sponsor/Chief Investigator (CI)]* will assume responsibility for submitting the reportable event(s) to EMD Serono 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 EMD Serono:

Fax: +49 6151 72 6914
OR
E-mail: ICSR_CT_GPS@merckgroup.com

Specifying:
- PROTOCOL Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

11.10. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate document. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Health Canada.

11.11. Safety Classifications

11.11.1. Relationship of Events to Study procedures

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study procedures:

Not related

An AE will be considered “not related” to study drug if there is not a reasonable possibility that the event has been caused by the drug under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the drug and the AE (e.g., the event occurred before administration of the drug), or the presence of a more likely alternative explanation for the AE.

Related

An AE will be considered “related” to the study drug if there is a possibility that the event may have been caused by the drug under investigation. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

11.11.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs from the National Cancer Institute-Common Terminology Criteria for Adverse Event, version 5.0 (NCI-CTCAE).

Mild (grade 1)

Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.

Moderate (grade 2)

Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.

Severe or life threatening (grade 3 or 4)

Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of drug, treatment for symptom(s) may be given and/or subject hospitalized.

11.12. Procedures for Handling Special Situations

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care.

11.13. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study procedure;
- Determine the seriousness, relationship, and severity of each event;
- Determine the onset and resolution dates of each event;
- Complete an SAE form for each serious event and fax it to Health Canada;
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Health Canada within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs to local ethics committees, as required by local law.

12. STATISTICAL STATEMENT AND ANALYTICAL PLAN

12.1. Sample Size Considerations

A convenience sample of thirty (30) patients is based on recruitment feasibility. This sample size will permit estimation of dichotomous outcome rates with margins of error of less than 18% (based on a significance level of 0.05) and estimation of continuous parameter means to within 0.36 standard deviations. This is an early stage study, so analysis will focus on descriptive statistics. Continuous parameters will be summarized by means and 95% confidence intervals or by medians and

interquartile ranges, as appropriate. Dichotomous outcomes will be summarized with point estimates of the rate, as well as 95% confidence intervals. Time-to-event data will be summarized using Kaplan-Meier curves.

12.2. Analyses

Complete analysis will be done when all patients have completed week 52 or end of study visit and repeated every 52 weeks thereafter. Interim descriptive analyses will be done when the first 10 patients have completed week 52 or the end of study visit and repeated when the first 20 patients have done so as well.

12.3. Efficacy data

12.3.1. Primary Endpoints

Safety and tolerability based on avelumab related adverse events leading to permanent or transient discontinuation of avelumab
Treatment related adverse events of special interest will include those of autoimmune origin (irAE).
The adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

12.3.2. Secondary Endpoints

Based on the results of Stupp *et al* (2005) (3), if avelumab had no effect then we would expect to see one-year overall survival and progression-free survival rates of 60% and 27%, respectively. We will conclude that we have preliminary evidence of benefit if either of our observed rates is significantly better based on a one-sided t-test at the 0.2 level of significance. With our projected sample of 30, this corresponds to concluding benefit if at least 21 patients survive to one-year or if at least 11 have survived without progression of disease.

Radiological tumor response will be graded according to the immunotherapy Response Assessment for Neuro-Oncology (iRANO)

Progression of Disease (PD) will be defined as a ≥25% increase on the 12 month MRI or CT scan in the sum of the product of the biperpendicular diameters of enhancing disease; or new lesions; or substantial worsened T2/FLAIR; or significant clinical neurological decline unexplained by a change in medication or concurrent comorbities. The SPD is the sum of the products of biperpendicular diameters of the measurable enhancing lesions (max 5 lesions).

Complete Response (CR) will be defined as the disappearance on the month 12 MRI or CT scan of all enhancing disease, no new lesions, with stable or improved T2/FLAIR; no more than physiological steroids; clinically stable or improved

Partial Response (PR) will be defined as a ≥50% decrease on the month 12 MRI or CT scan in the sum of the product of the biperpendicular diameters of enhancing disease, no new lesions, stable or improved T2/FLAIR, stable (>2 months) or decreased steroid dose, clinically stable or improved

Stable Disease (SD) will be defined at 12 months when a patient do not qualify for complete response, partial response, or progressive disease, stable or improved T2/FLAIR; stable (>2 months) or decreased steroid dose, clinically stable or improved

Overall survival (OS) will be defined as the time from baseline to the date of death from any cause.

Objective Response Rate (ORR) will be defined the number of patients with either CR or PR divided by the total number of patients.

Progression Free Survival (PFS) will be defined as the time from baseline to documented PD or death from any cause.
Results will be stratified according to MGMT status, baseline age (>50yrs), baseline Karnofsky performance score (score of 100), radical tumor resection vs biopsy, primary versus secondary GBM,

12.3.3. Exploratory

The incidence of PD-L1 expression on tumor cells and microglia/macrophages within the tumor will be determined and correlated to OS and PFS and other iRANO endpoints

The histological immunoscore will be determined and tested for association with OS, PFS, and other iRANO endpoints using logistic regression.

The association between 12 months OS and PFS with baseline neurocognitive function as measured by the evoked potential P300 (normal), the baseline corticosteroid dose, the average daily corticosteroid dose over the whole study duration, the extent to which patients complete the full 6 cycles of temozolomide based on temozolomide toxicity and the incidence and severity of treatment related irAE's will be tested using logistic regression.

The change if any in histological markers on tissue obtained from repeat resection

The estimation of the time period in which radiological progression was seen in clinically stable patients whose imaging was subsequently followed by radiological stabilization or regression
The estimation of the time period in clinically stable patients before radiological evidence of tumor regression occurred

The change in P300 will be determined and correlated with clinical outcomes as per iRANO.

13. ETHICAL REQUIREMENTS

The Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and Good Clinical Practice (GCP) guidelines, and must also conduct the study according to local regulations.

The tripartite harmonised ICH Guideline was finalized under *Step 4* in May 1996. This Good Clinical Practices document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. GCPs cover aspects of monitoring, reporting and archiving of clinical trials.

13.1. Local Regulations/Declaration of Helsinki

The Investigator must follow the recommendations contained in the Declaration of Helsinki or with the laws and regulations of the country in which the research is conducted. The Declaration of Helsinki was amended at the 48th General Assembly in Somerset West, Republic of South Africa, dated October 1996 (see Section 21).

13.2. Ethics Committee

This protocol and any accompanying material provided to the subject (such as subject information sheets, advertising or compensation given), will be submitted by the investigator to an Institutional Review Board. The Investigator must obtain written IRB/IEC approval of the protocol, ICF, and other required study documents prior to starting the study.

Any modifications made to the protocol after receipt of Institutional Review Board approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

13.3. No objection Letter (NOL)

A clinical trial involving human subjects planned for conduct in Canada must comply with the regulations stipulated by the food and drugs Act, including the Food and drug regulations, or the Medical Devices regulations and be authorized by Health Canada (HC) through issue of a NOL.

13.4. Subject Information and Consent

Prior to any evaluations under this protocol, written informed consent must be obtained from the subject in accordance with local practice and regulations. The background of the proposed study and the benefits and risks of the procedures and study must be explained to the subject. A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent

must also be documented in the subject's medical record prior to any evaluations under this protocol.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

13. 5. Subject Data Protection

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

14. ADMINISTRATIVE PROCEDURES

14.1. Study documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: Investigator's Study File and subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, IRB approval, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc. The Investigator will be responsible for keeping the Investigator File updated and ensuring that all required documents are filed during and after the study.

Subject clinical source documents would include patient hospital/clinic records, physician and nurse's notes, appointment book, original laboratory reports, other tests, and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrolment logs.

14.2. Monitoring of the Study

Monitoring of the study will be performed by an independent monitor.

14.3. Study Funding

Merck Serono via an unrestricted grant will financially support the work of the Investigator as it pertains to the conduct of this study. All financial details are provided in the separate contract between the Investigator and Sponsor.

15. FURTHER REQUIREMENTS AND GENERAL INFORMATION

No CRO will be involved in this study.

15.1. Study Committees

An external safety monitoring board and a separate internal data monitoring committee will be established.

15.2. Changes to Final Study Protocol

All protocol amendments must be submitted to the IRB/IEC. Protocol modifications that affect the scientific quality of the study must be approved by the IRB/IEC and submitted to the appropriate regulatory authorities before implementation of such modifications to the conduct of the study. In the event of a protocol modification, the subject consent form may require similar modifications.

15.3. Record Retention

The Principal Investigator(s) must maintain all Essential Documents (as listed in the ICH Guideline for GCP) in accordance with all local laws regarding retention of records for at least 25 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

15.4. Publication of data

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Sponsor prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator. Details are included in the clinical trial agreement for this study.

15.5. Study Completion

The IRB/IEC must be notified of completion or termination of this study. In accordance with necessary timelines, the Investigator must provide a final clinical summary report to the IRB/IEC. The Investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC.

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17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature and Date

_____

Investigator's Name (Print)

18. APPENDIX

Appendix 1

iRANO algorithm

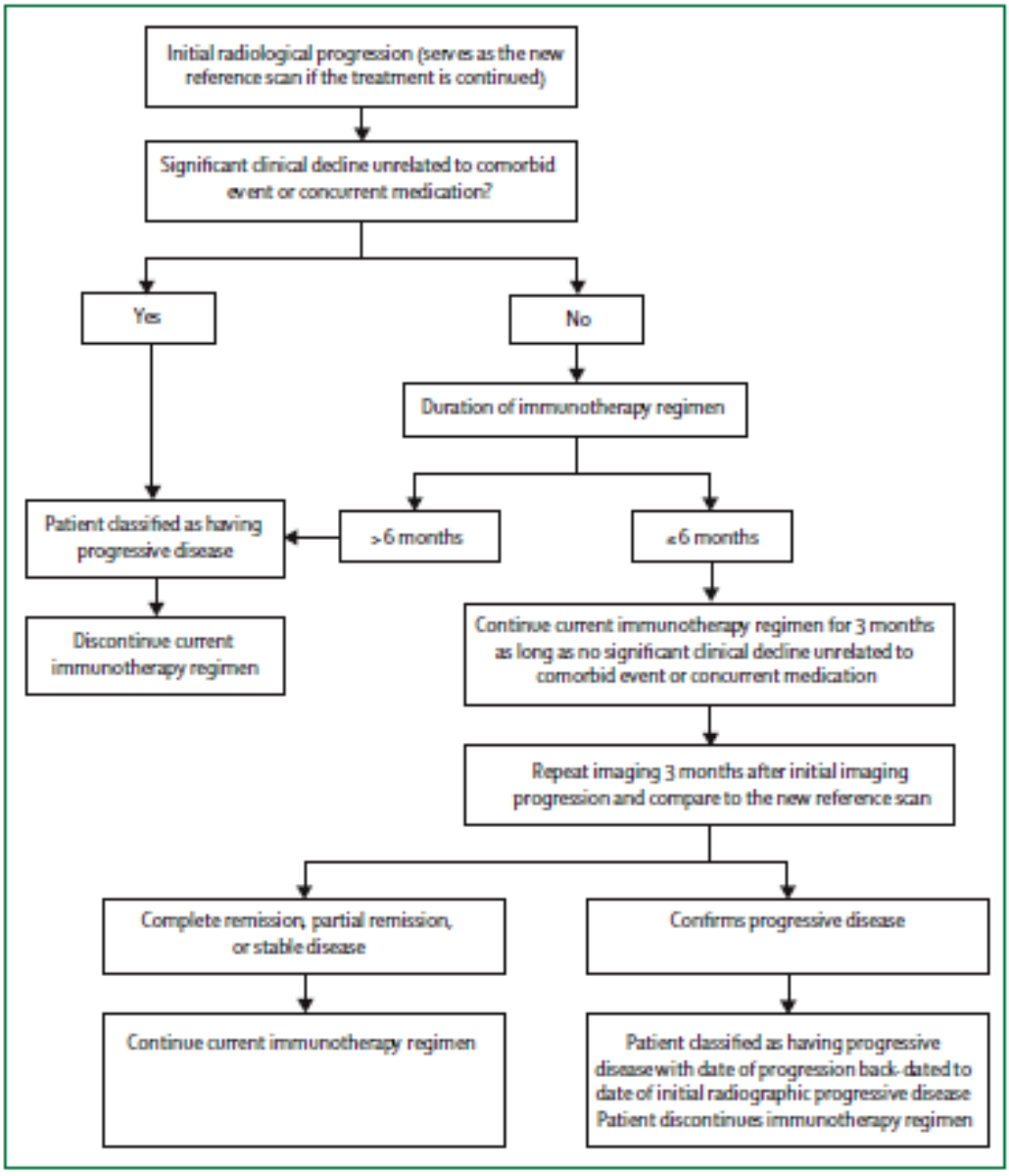

Figure 3: **iRANO treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy**
iRANO=immunotherapy Response Assessment in Neuro-Oncology.

APPENDIX 2

Karnofsky performance status scale

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

KARNOFSKY PERFORMANCE STATUS SCALE
DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	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.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	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 personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX 3

MRI Parameters

The MR imaging will be performed on a 1.5 T scanner (GE) in sagittal T1 SE, axial T2 TSE fatsat, axial FLAIR, and axial T1 TSE. After IV gadolinium injection, additional images will be obtained in axial T1 TSE and sagittal 3D T1 (FSPGR) with axial and coronal reconstructions. Details of the parameters are presented in tables below (table 4).

Table 4: Details of parameters

Protocol: 16CH AVELUMAB GBM

3-pl T2* FGRE S

PATIENT POSITION		**IMAGING PARAMETERS**	
Patient Entry	*Head First*	Imaging Mode	*2D*
Patient Position	*Supine*	Pulse Sequence	*Gradient Echo*
Coil Configuration	*HNS Head*	Imaging Options	*Seq, Fast*
Plane	*3-PLANE*	Acceleration Factor	*1.00*
Series Description	*3-pl T2* FGRE S*		
SCAN RANGE		**IMAGE ENHANCE**	
FOV	*24.0*	Filter Choice	*None*
Slice Thickness	*5.0*		
Slice Spacing	*5.0*		
ACQ TIMING		**GATING/TRIGGER**	
Freq	*256*	Auto Trigger Type	*Off*
Phase	*128*		
Freq DIR	*Unswap*		
NEX	*1.00*		
Phase FOV	*1.00*		
Auto Shim	*Off*		
Phase Correction	*No*		
FMRI		**MULTI-PHASE**	
PSD Trigger	*Internal*	# of Acquisition	*0*
Slice Order	*Interleaved*	Seperate Series	*0*
View Order	*Bottom/Up*	Mask Phase	*0*
# of Repetitions REST	*0*	Mask Pause	*0*
# of Repetitions ACTIVE	*0*		
SAT		**ASSET**	
Tag Type	*None*	Slice Acceleration Factor	*1.00*
		Phase Acceleration Factor	*1.00*
TRICKS		**CONTRAST**	
Pause On/Off	*On*	Contrast Yes/No	*No*
Auto Subtract	*0*		
Auto SCIC	*Off*		
MULTI-STATION			
Number of Stations	*0*		
Station Number	*0*		

3-pl T2* FGRE S

Protocol: 16CH AVELUMAB GBM

Calibration

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*HNS Head*
Plane	*AXIAL*
Series Description	*Calibration*

SCAN TIMING	
Number of Echoes	*1*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

ASSET	
Slice Acceleration Factor	*1.00*
Phase Acceleration Factor	*1.00*

CONTRAST	
Contrast Yes/No	*No*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*Gradient Echo*
Imaging Options	*Fast, Calib*
Acceleration Factor	*1.00*

SCAN RANGE	
FOV	*30.0*
Slice Thickness	*6.0*
Slice Spacing	*0.0*

ACQ TIMING	
Freq DIR	*R/L*
Auto Shim	*Auto*
Phase Correction	*No*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*Off*

MULTI-STATION	
Number of Stations	*0*
Station Number	*0*

Calibration

Protocol: 16CH AVELUMAB GBM

SAG T1 SE

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*HNS Head*
Plane	*OBLIQUE*
Series Description	*SAG T1 SE*

SCAN TIMING	
TE	*Min Full*
Number of Echoes	*1*
TR	*600.0*
Echo Train Length	*3*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

ASSET	
Slice Acceleration Factor	*1.00*
Phase Acceleration Factor	*1.00*

TRACKER	
Tracker Length	*200.0*
Tracker Thickness	*20.0*

MULTI-STATION	
Number of Stations	*0*
Station Number	*0*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*FSE-XL*
Imaging Options	*Fast*
Acceleration Factor	*1.00*

SCAN RANGE	
FOV	*22.0*
Slice Thickness	*5.0*
Slice Spacing	*1.0*

ACQ TIMING	
Freq	*512*
Phase	*224*
Freq DIR	*S/I*
NEX	*2.00*
# of Acq. Before Pause	*0*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*Yes*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*2*

CONTRAST	
Contrast Yes/No	*No*

SAG T1 SE

Protocol: 16CH AVELUMAB GBM

AX T2 FS FSE

PATIENT POSITION	
Patient Entry	Head First
Patient Position	Supine
Coil Configuration	HNS Head
Plane	OBLIQUE
Series Description	AX T2 FS FSE

SCAN TIMING	
TE	125.0
Number of Echoes	1
TR	6434.0
Echo Train Length	15
Receiver Bandwidth	31.25

IMAGE ENHANCE	
Filter Choice	None

GATING/TRIGGER	
Auto Trigger Type	Off

FMRI	
PSD Trigger	Internal
Slice Order	Interleaved
View Order	Bottom/Up
# of Repetitions REST	0
# of Repetitions ACTIVE	0

SAT	
Tag Type	None
Fat/Water Saturation	Fat

TRICKS	
Pause On/Off	On
Auto Subtract	0
Auto SCIC	2

CONTRAST	
Contrast Yes/No	No

IMAGING PARAMETERS	
Imaging Mode	2D
Pulse Sequence	FRFSE-XL
Imaging Options	FC, TRF, Fast, FR
Acceleration Factor	1.00

SCAN RANGE	
FOV	23.0
Slice Thickness	5.0
Slice Spacing	0.0

ACQ TIMING	
Freq	512
Phase	320
Freq DIR	A/P
NEX	2.00
Phase FOV	0.75
Auto Shim	Auto
Phase Correction	Yes
Flow Direction Compensation	Slice

USER CVS	
User CV7	1.00
User CV19	1.00

MULTI-PHASE	
# of Acquisition	1
Seperate Series	0
Mask Phase	0
Mask Pause	0

ASSET	
Slice Acceleration Factor	1.00
Phase Acceleration Factor	1.00

TRACKER	
Tracker Length	200.0
Tracker Thickness	20.0

MULTI-STATION	
Number of Stations	0
Station Number	0

AX T2 FS FSE

Protocol: 16CH AVELUMAB GBM

T2 FLAIR

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*HNS Head*
Plane	*OBLIQUE*
Series Description	*T2 FLAIR*

SCAN TIMING	
TE	*120.0*
TR	*9500.0*
TI	*2250*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
SAT Location	*I*
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*On*

CONTRAST	
Contrast Yes/No	*No*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*T2flair*
Imaging Options	*TRF, Fast, ZIP512*
Acceleration Factor	*1.00*

SCAN RANGE	
FOV	*23.0*
Slice Thickness	*5.0*
Slice Spacing	*0.0*

ACQ TIMING	
Freq	*352*
Phase	*224*
Freq DIR	*A/P*
NEX	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV3	*2.00*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

ASSET	
Slice Acceleration Factor	*1.00*
Phase Acceleration Factor	*1.00*

TRACKER	
Tracker Length	*200.0*
Tracker Thickness	*20.0*

MULTI-STATION	
Number of Stations	*0*
Station Number	*0*

T2 FLAIR

Protocol: 16CH AVELUMAB GBM

PRE AX T1 FSE

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*HNS Head*
Plane	*OBLIQUE*
Series Description	*PRE AX T1 FSE*

SCAN TIMING	
TE	*Min Full*
Number of Echoes	*1*
TR	*617.0*
Echo Train Length	*3*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

MULTI-PHASE	
# of Acquisition	*3*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

ASSET	
Slice Acceleration Factor	*1.00*
Phase Acceleration Factor	*1.00*

CONTRAST	
Contrast Yes/No	*No*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*FSE-XL*
Imaging Options	*TRF, Fast*
Acceleration Factor	*1.00*

SCAN RANGE	
FOV	*23.0*
Slice Thickness	*5.0*
Slice Spacing	*0.0*

ACQ TIMING	
Freq	*512*
Phase	*224*
Freq DIR	*A/P*
NEX	*2.00*
# of Acq. Before Pause	*0*
Phase FOV	*0.75*
Auto Shim	*Auto*
Phase Correction	*Yes*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
SAT Location	*I*
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*2*

MULTI-STATION	
Number of Stations	*0*
Station Number	*0*

PRE AX T1 FSE

Protocol: 16CH AVELUMAB GBM

POST AX T1 FSE

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*HNS Head*
Plane	*OBLIQUE*
Series Description	*POST AX T1 FSE*

SCAN TIMING	
TE	*Min Full*
Number of Echoes	*1*
TR	*617.0*
Echo Train Length	*3*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*

MULTI-PHASE	
# of Acquisition	*3*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

ASSET	
Slice Acceleration Factor	*1.00*
Phase Acceleration Factor	*1.00*

CONTRAST	
Contrast Yes/No	*Yes*

IMAGING PARAMETERS	
Imaging Mode	*2D*
Pulse Sequence	*FSE-XL*
Imaging Options	*TRF, Fast*
Acceleration Factor	*1.00*

SCAN RANGE	
FOV	*23.0*
Slice Thickness	*5.0*
Slice Spacing	*0.0*

ACQ TIMING	
Freq	*512*
Phase	*224*
Freq DIR	*A/P*
NEX	*2.00*
# of Acq. Before Pause	*0*
Phase FOV	*0.75*
Auto Shim	*Auto*
Phase Correction	*Yes*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

SAT	
SAT Location	*I*
Tag Type	*None*

TRICKS	
Pause On/Off	*On*
Auto Subtract	*0*
Auto SCIC	*2*

MULTI-STATION	
Number of Stations	*0*
Station Number	*0*

POST AX T1 FSE

Protocol: 16CH AVELUMAB GBM

POST SAG 3DFSPGR T1

PATIENT POSITION	
Patient Entry	Head First
Patient Position	Supine
Coil Configuration	HNS Head
Plane	OBLIQUE
Series Description	POST SAG 3DFSPGR T1

SCAN TIMING	
Flip Angle	15
TE	Minimum
TI	450
Receiver Bandwidth	15.63

IMAGE ENHANCE	
Filter Choice	None

GATING/TRIGGER	
Auto Trigger Type	Off

FMRI	
PSD Trigger	Internal
Slice Order	Interleaved
View Order	Bottom/Up
# of Repetitions REST	0
# of Repetitions ACTIVE	0

SAT	
Tag Type	None

TRICKS	
Pause On/Off	On
Auto Subtract	0
Auto SCIC	2

MULTI-STATION	
Number of Stations	0
Station Number	0

IMAGING PARAMETERS	
Imaging Mode	3D
Pulse Sequence	SPGR
Imaging Options	Fast, IrP
Acceleration Factor	1.00

SCAN RANGE	
FOV	25.0
Slice Thickness	1.5
Location per Slab	108
Overlap Locations	0

ACQ TIMING	
Freq	256
Phase	224
Freq DIR	S/I
NEX	1.00
Phase FOV	0.85
Auto Shim	Auto
Phase Correction	No

USER CVS	
User CV6	1.00
User CV23	100.00

MULTI-PHASE	
# of Acquisition	0
Seperate Series	0
Mask Phase	0
Mask Pause	0

ASSET	
Slice Acceleration Factor	1.00
Phase Acceleration Factor	1.00

CONTRAST	
Contrast Yes/No	Yes

POST SAG 3DFSPGR T1

APPENDIX 4:

From Temozolomide's product monograph

TEMOZOLOMIDE DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
Adults Patients with Newly Diagnosed Glioblastoma Multiforme:

Concomitant Phase
TEMODAL® is administered at a dose of 75 mg/m2 daily for 42 days concomitant with radiotherapy (60 Gy administered in 30 fractions) followed by maintenance TEMODAL® for 6 cycles. No dose reductions are recommended; however, dose interruptions may occur based on patient tolerance. The TEMODAL® dose can be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥1.5 x 109/L; platelet count ≥100 x109/L; common toxicity criteria (CTC) non-hematological toxicity Grade ≤1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. TEMODAL® dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in Table 7.

Table 7. TEMODAL® Dosing Interruption or Discontinuation During Concomitant Radiotherapy and TEMODAL®

Toxicity	**TEMODAL® Interruptiona**	**TEMODAL® Discontinuation**
Absolute Neutrophil Count	≥0.5 and <1.5 x 109/L	<0.5 x 109/L
Platelet Count	≥10 and <100 x 109/L	<10 x 109/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TEMODAL® could be continued when all of the following conditions were met: absolute neutrophil count ≥1.5 x 109/L; platelet count ≥100 x 109/L; CTC non-hematological toxicity Grade ≤1 (except for alopecia, nausea, vomiting).
CTC = Common Toxicity Criteria.

Maintenance Phase
Four weeks after completing the TEMODAL® + RT (Radiotherapy) phase, TEMODAL® is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥1.5 x 109/L, and the platelet count is ≥100 x 109/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. Dose reductions during the maintenance phase should be applied according to Tables 8 and 9.
During treatment a complete blood count should be obtained on day 22 (21 days after the first dose of TEMODAL®). The TEMODAL® dose should be reduced or discontinued according to Table 9.

Table 8. TEMODAL® Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2–6 in absence of toxicity

Table 9. TEMODAL® Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TEMODAL® by 1 Dose Level[a]	Discontinue TEMODAL®
Absolute Neutrophil Count	<1.0 x 10^9/L	See footnote b
Platelet Count	<50 x 10^9/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4b

a: TEMODAL® dose levels are listed in Table 8.
b: TEMODAL® is to be discontinued if dose reduction to <100 mg/m2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.
CTC = Common Toxicity Criteria.

Malignant Gliomas Showing Recurrence or Progression after Standard Therapy:
Adult patients: In patients previously untreated with chemotherapy, TEMODAL® is administered at a dose of 200 mg/m2 once daily for 5 days per 28-day cycle. For patients previously treated with chemotherapy, the initial dose is 150 mg/m2 once daily for 5 days, to be increased in the second cycle to 200 mg/m2 once daily for 5 days, providing there is no hematologic toxicity (see **WARNINGS AND PRECAUTIONS**).
In the reference controlled trial of GBM, the majority of patients treated with TEMODAL® (90%) received more than one cycle and 22% of patients received 6 or more cycles. These patients received a total of 484 cycles of TEMODAL® in total; 60% of cycles at 200 mg/m2/day and 36% at 150 mg/m2/day. In the single arm AA trial, 93% of patients received more than one cycle and 25% of patients continued on study for 12 months or greater. Eighty-eight percent of patients were receiving either their initial dose or a higher dose at the last cycle. However, limited experience is available on the prolonged use of TEMODAL® in this patient population.
TEMODAL® therapy can be continued until disease progression.

APPENDIX 5:

ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.