PROTOCOL TITLE:

Prospective Randomized Placebo-Controlled Trial of SurVaxM Plus Adjuvant Temozolomide for Newly Diagnosed Glioblastoma (SURVIVE)

PROTOCOL NUMBER: I-813720

IND NUMBER: 27050

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PROTOCOL SIGNATURE PAGE

SPONSOR SIGNATURE

I have carefully read the protocol, Prospective, Randomized Placebo-Controlled Trial of SurVaxM Plus Adjuvant Temozolomide for Newly Diagnosed Glioblastoma (Survive) and confirm this is the approved current version.

Sponsor's Signature	Date (DD/MMM/YYYY)
Printed Name	

INVESTIGATOR'S SIGNATURE

I have carefully read this protocol, Prospective, Randomized Placebo-Controlled Trial of SurVaxM Plus Adjuvant Temozolomide for Newly Diagnosed Glioblastoma (Survive), and commit to conduct the study as outlined herein, in accordance with the International Council for Harmonisation (ICH), Good Clinical Practices (GCPs) and the Declaration of Helsinki, and comply with the obligations and requirements of the Clinical Investigator and other requirements as listed in Title 21 of the United States Code of Federal Regulations (CFR) and other applicable regulations.

Investigator's Signature	Date (DD/MMM/YYYY)
Printed Name	Name of Institution/Research Facility
Phone Number	Email Address

SERIOUS ADVERSE EVENT (SAE) REPORTING

CONTACT CRO WITHIN 24 HOURS OF LEARNING OF ANY SERIOUS ADVERSE EVENT. IF THE SAE IS FATAL OR LIFE THREATENING, THE SPONSOR AND CRO MUST BE INFORMED IMMEDIATELY.

Contact the Medical Monitor, CRO and Sponsor as described below, and complete a SAE report form:

CALL, EMAIL OR FAX SAE REPORT FORM TO:	MEDICAL MONITOR
Attn: ProPharma Group Clinical Safety **Fax: (866) 681-1063** **Email: *clinicalsafety@propharmagroup.com***	**Attn: Jennifer Neal-Jimenez, MD, MSB, MS, CCRP** **Phone:** +1 813-598-2981 **Email: JNeal@TD2inc.com**

For reporting of all serious adverse events, Investigators must fax or email all completed pages of the SAE report form within 24 hours to the following:

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FAX #: (866) 681-1063

Email: *clinicalsafety@propharmagroup.com*

To discuss SAE with the Medical Monitor, contact Dr. Jennifer Neal-Jimenez at the numbers provided above. Follow-up information to SAEs must be provided to TD2 (the CRO) within 24 hours of Investigator awareness.

1 SYNOPSIS

Study Title:	Prospective Randomized Placebo-Controlled Trial of SurVaxM Plus Adjuvant Temozolomide for Newly Diagnosed Glioblastoma (SURVIVE)
Sponsor:	MimiVax, LLC
Protocol Number	I 813720
Version Number	3.1
Date	03Mar2021
Primary Objective:	• To compare overall survival (OS) in patients with newly diagnosed glioblastoma between treatment arms A and B.
Secondary Objectives:	• To tabulate the number and type of grade 3 and grade 4 toxicities, according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAEs) Version 5. • To compare progression free survival in patients with newly diagnosed glioblastoma between treatment arms A and B. • To compare treatment-associated overall survival at pre-specified time points (OS-15, OS-18 and OS-24) between treatment arms A and B. • To compare treatment-associated progression-free survival at pre-specified time points (PFS-3, PFS-6 and PFS-12) between treatment arms A and B.
Exploratory and Scientific Objectives	• To evaluate the predictive value of perfusion-weighted imaging in assessing pseudo-progression and post-vaccination enhancement in patients receiving SurVaxM. • To evaluate the objective image-based tumor response rate (applicable only for patients with evaluable disease at study entry as defined by RANO criteria). • To evaluate molecular predictors of response to SurVaxM, including MGMT methylation status, anti-survivin immunoglobin titers, survivin-specific CD8+ responses, tumor survivin expression levels and other molecular tumor tissue markers.
Study Design:	This is a prospective, randomized, placebo-controlled, multicenter study of patients with newly diagnosed glioblastoma (nGBM) to evaluate a peptide vaccine (SurVaxM) in emulsion with Montanide given together with locally administered sargramostim plus adjuvant oral temozolomide (TMZ) (Arm A) versus saline-Montanide emulsion with locally administered saline (instead of sargramostim) plus adjuvant oral temozolomide (TMZ) (Arm B).

	Patients will be randomized 3:2 = A:B to treatment with SurVaxM in emulsion with Montanide plus sargramostim (local injection) and standard-of-care TMZ (Arm A), or placebo (saline in emulsion with Montanide) plus saline (local injection) and standard-of-care TMZ (Arm B). Randomization is described in **Section 6.1.** To be eligible to participate, patients must have undergone a contrast-enhanced, post-operative MRI scan within 72 hours of surgical resection documenting ≤1 cm^3 of residual contrast enhancement (i.e., gross-total or near-total resection). This must be followed by fractionated radiation therapy with concurrent temozolomide (chemoradiation) according to established Stupp protocol. MRI must be performed following completion of chemoradiation to ensure no tumor recurrence or progression. All patients must undergo randomization within 16 weeks of surgical tumor resection in order to participate. Local radiology reviews will be used for clinical decision making on the study. Central radiology reviews will be response criteria that are used for statistical determination of progression-free survival.
Duration:	Study duration is expected to be 36 months. Enrollment at up to 20 centers is expected to be 18 months, with follow-up of the last patient enrolled being as long as 18 months.
Planned Total Sample Size:	This trial is designed as a parallel-groups, 3:2 randomized placebo-controlled trial of SurVaxM as add-on therapy to standard of care temozolomide for newly diagnosed glioblastoma. The sample size will be n_1=159 in the SurVaxM arm and n_2=106 in the control arm for a total sample size of n_1+n_2=265.
Study Drug Administration:	***All patients will receive the standard of care, adjuvant treatment with TMZ.*** There are three active treatment phases on this study: Vaccine Priming (VP) phase; adjuvant TMZ phase; and Vaccine Maintenance (VM) phase. Based on the randomization, either four (4) "priming doses" of SurVaxM in emulsion with Montanide plus sargramostim (local injection) or four (4) "priming doses" of placebo (saline in emulsion with Montanide) plus saline (local injection) will be administered every 2 weeks (± 3 days). The first "priming dose" of SurVaxM in Montanide plus sargramostim or placebo must occur within 7-28 days after completion of chemoradiation unless pseudo-progression is suspected**.** At least one priming dose must be administered in advance of initiating the standard of care adjuvant treatment with TMZ. Adjuvant TMZ should be started ideally within 28 days (± 14 days) of completion of chemoradiation, or as soon as feasible when residual effects from the chemoradiation are ≤ Grade 2 (up to 8 weeks also acceptable). A total of four (4) priming doses of SurVaxM in Montanide

	plus sargramostim ("SurVaxM/sagramostim") or placebo in Montanide/saline ("Placebo/Placebo") will be administered every two weeks (± 3 days) during the priming phase, with subsequent dosing every 8 weeks (± 1 week) during the vaccine maintenance phase. The preferred location for subcutaneous dosing will be the deltoid area, alternating between the left and right deltoid sites with each SurVaxM/sargramostim or Placebo/Placebo dosing as outlined in **Section 8.2.1**. As per standard of care, adjuvant TMZ should be given for at least 6 cycles (5 daily doses every 28 days) if it is tolerated, but not more than 12 cycles. After the priming doses, SurVaxM/sargramostim or Placebo/Placebo will be administered every 8 weeks (± 1 week) until tumor progression or for a maximum of 24 months, irrespective of whether treatment with adjuvant TMZ is ongoing.
Key Inclusion Criteria:	To be included in this study, participants must meet the following criteria: 1 Age ≥ 18 years of age. 2 Have a Karnofsky performance status ≥ 70 (i.e., the patient must be able to care for him/herself with occasional help from others; refer to **Appendix A**). 3 Pathologically confirmed diagnosis of glioblastoma of the cerebrum. 4 The result of tumor MGMT methylation study must be available. 5 The result of tumor IDH-1 mutation test must be available. 6 Have the following clinical laboratory values obtained within 14 days prior to registration: o Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L o Platelets ≥ 100 x 10^9/L o Hemoglobin (Hgb) ≥ 9.0 g/dL o Total bilirubin: ≤ 1.5 x ULN o ALT and AST ≤ 4.0 x ULN o Creatinine ≤ 1.8 mg/dL o Prothrombin time (PT) within 1.5x normal limits o Activated partial thromboplastin time (aPPT) within 1.5x control o International Normalized Ration (INR) less than or equal to 1.5x control 7 Patient must have no active bleeding or pathological condition that carries a high risk of bleeding (e.g., coagulopathy)

	8 Available results from a contrast-enhanced, post-operative brain MRI that was completed within 72 hours after surgery documenting either: 1) gross total resection consisting of no gadolinium enhancement; or 2) near-total resection consisting of either $\leq 1\ cm^3$ nodular (i.e. volumetric) enhancement or $\leq 100\ mm^2$ in cross sectional area (i.e. linear enhancement). **Note:** Patients who undergo either stereotactic biopsy or open biopsy for tissue diagnosis, or partial tumor resection, and who subsequently have a definitive surgical resection may still be eligible for inclusion, provided that randomization can occur within 16 weeks of the date of surgical resection. To be eligible, such patients must still meet post-operative imaging entry criteria as defined in item #8 above. 9 Patients must have completed initial radiation therapy with TMZ (chemoradiation) according to established Stupp protocol (Stupp, 2005) for the treatment of their glioblastoma (i.e., completed 6-week course of RT and completed ≥ 75% of a course of concurrent TMZ chemotherapy). 10 Patients must be randomized within 16 weeks of surgical resection of their newly diagnosed glioblastoma. 11 No evidence of progressive disease at the post-chemoradiation timepoint based on changes in: neurologic exam, corticosteroid use or radiographic progression (i.e., baseline MRI evaluation). See **Section 14.5** for suspected pseudo-progression. 12 Participants of child-bearing potential (not surgically sterile or post-menopausal) must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and have a negative pregnancy test prior to starting study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. 13 Dexamethasone dose less than or equal to 4 mg daily at time of study enrollment. Every reasonable effort should be made to reduce the dose of corticosteroids to the absolute minimum dose required to control neurologic symptoms prior to receiving SurVaxM. 14 Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.
Key Exclusion Criteria	Participants with any of the following will be excluded from this study: **1** Recurrent or progressive glioblastoma.

	2 Gliosarcoma, anaplastic astrocytoma, oligodendroglioma, ependymoma, low grade glioma or any histology other than glioblastoma **3** Multicentric glioblastoma or glioblastoma involving the brainstem or cerebellum, or leptomeningeal or spinal extension present at diagnosis. **4** Residual contrast enhancement $> 1\ cm^3$ on post-operative scan obtained within 72 hours of surgery. **5** Absence of MRI obtained within 72 hours of craniotomy documenting $\leq 1\ cm^3$ contrast-enhancing tumor. **6** Patients who elect to have Optune therapy (Tumor Treating Fields) are not eligible to participate in this trial. **7** Patient has had non-standard radiation therapy for glioblastoma (i.e., whole brain radiation therapy, gamma knife or LINAC stereotactic radiosurgery). **8** Prior or concurrent immunotherapy for brain tumor, including immune checkpoint inhibitors (pembrolizumab, nivolumab or ipilimumab) or other cancer vaccine therapy. **9** Prior or concurrent treatment with bevacizumab. **10** Patients with serious concurrent infection or medical illness, which in the treating physician's opinion would jeopardize the ability of the patient to receive the treatment outlined in this protocol with reasonable safety. **11** History of tuberculosis or other granulomatous disease. **12** Patient is pregnant or breast-feeding. **13** Patient has received any other chemotherapeutic agent or investigational drug in addition to standard of care radiation therapy with concomitant temozolomide (chemoradiation per Stupp protocol). **14** Patient with concurrent or prior malignancy is ineligible unless he or she has had curatively treated carcinoma-in-situ or basal cell carcinoma of the skin. **15** Patients who have had repeat craniotomy for tumor therapy after receiving RT and TMZ treatment (i.e., chemoradiation). **16** Patients who have had surgical implantation of carmustine (Gliadel) wafers are not eligible to participate in this study. **17** Known history of systemic autoimmune disorder. **18** Known human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS) related illness or other serious medical illness.

	19 Patient has a contraindication to MRI scans or to gadolinium contrast agent **20** Patient has a contraindication to temozolomide. **21** Patient is unwilling or unable to follow protocol requirements. **22** Patient has received any other investigational treatment for the glioblastoma. **23** Any condition which in the Investigator's opinion makes the candidate unsuitable to receive the study drug or protocol procedures.
Pre-Treatment Assessments:	Screening Period (Up to up to 16 weeks prior to Day 1): • Obtain a signed informed consent form • Obtain results from brain MRI scan obtained within 72 hours following craniotomy (evaluated for residual contrast-enhancing tumor) • Perform baseline MRI following chemoradiation (evaluated by RANO for continuing eligibility) • Medical and surgical history • Full physical examination • Neurologic examination • Vital signs (temperature, blood pressure, respiratory rate and pulse rate) • Height • Weight • Karnofsky Performance Status • Prior and concomitant medication assessment • Treatment assessment • Serum or urine pregnancy test (for nonsterile women of childbearing potential) • Laboratory Parameters o Serum chemistries o CBC with differential o Baseline immune profiling (PBMCs, ADA and HLA) o Coagulation parameters (PT, aPPT, INR) o Urinalysis • HLA typing • Secure archival tissue and blood for exome sequencing • Conduct eligibility assessment
Treatment Assessments:	There are three treatment phases on this study: a vaccine priming (VP) phase in which active drug (Arm A) or placebo (Arm B) will be administered every two weeks, adjuvant temozolomide (TMZ) phase as standard of care for both active and placebo arms, and a vaccine maintenance (VM) phase in which active drug or placebo will be administered every 8 weeks. The

	adjuvant temozolomide phase may overlap the end of the VP phase and will overlap all or part of the maintenance phase as described below.
	
	Vaccine Priming (VP) Phase: Doses VP1, VP2, VP3, VP4 every 14 days (± 3 days) with VP1 initiated within 7 to 28 days of completion of chemoradiation as described in Previous Treatments.
	
	VP Dosing Visits and Telephone Follow up:
	VP Dosing: The following assessments will be performed for each of the 4 VP visits:
	• Symptom directed physical exam
	• Assess baseline signs and symptoms (VP1 visit only)
	• Vital signs (temperature, blood pressure, and pulse rate)
	• Weight
	• Karnofsky Performance Status
	• Concomitant medication and treatment assessment
	• Laboratory Parameters
	  o Serum chemistries
	  o CBC with differential
	  o Immune profiling (PBMCs and ADA) (VP1 visit only)
	• AE assessment
	• Administer SurVaxM in emulsion with Montanide plus sargramostim (local injection) or placebo (saline in emulsion with Montanide) plus saline (local injection)
	• Additional standard of care MRIs that may be obtained in the time between the VP doses and the first MRI in the VM phase should be collected.
	• Injection Site Assessment to evaluate for reaction
	
	Telephone Follow up 3 – 5 days after each VP dose administration to collect reaction data
	• Patient self-evaluates the injection site for skin reaction and reports to research staff in telephone follow up.
	
	NOTE: Following the four (4) VP doses, the patient will move directly into the Vaccine Maintenance Phase.
	
	Adjuvant TMZ will be started ideally 28 days (± 14 days) of completion of the chemoradiation, or as soon as feasible when residual effects from the chemoradiation are ≤ Grade 2 (up to 8 weeks also acceptable), but after at least one VP dose. As per standard of care, adjuvant TMZ should be given for at least 6 cycles, as tolerated, but not more than 12 cycles. TMZ is dosed on the first five (5) consecutive days of a 28-day schedule as outlined in **Section 8.3**. If feasible, the initiation of TMZ should be aligned with one of

	the vaccine priming or vaccine maintenance doses; however, the initiation of adjuvant TMZ should not be significantly withheld when patient becomes eligible. Within the assigned visit windows, over time the TMZ visits should be aligned with VM visits for patient convenience, if possible. The following assessments will be performed on Day 1 of all TMZ cycles, except as outlined below. **TMZ Day 1** (All Cycles) (± 3 days) • Symptom-directed physical exam • Vital signs (temperature, blood pressure and pulse rate) • Weight • Karnofsky Performance Status • Concomitant medication and treatment assessment • Laboratory Parameters o Serum chemistries o CBC with differential o Immune profiling (PBMCs and ADA) (TMZ Cycle 1 only) • AE assessment NOTE: If TMZ dosing coincides with vaccine dosing (priming and maintenance), assessments that are required by both schedules can be conducted only once. **TMZ Day 21** (All Cycles) (± 3 days) • Laboratory Parameters o CBC with differential **Vaccine Maintenance (VM) Phase** will be started 8 weeks (± 1 week) after the fourth (4^{th}) Vaccine Priming dose. VM doses will be administered every 8 weeks (± 1 week) **VM Day 1 (All Cycles)** • Symptom Directed Physical Exam • Vital signs (temperature, blood pressure, and pulse rate) • Weight • Karnofsky Performance Status • Concomitant medication and treatment assessment • Serum or urine pregnancy test (for nonsterile women of childbearing potential) • Laboratory Parameters o Serum chemistries o CBC with differential o Coagulation parameters (PT, aPPT, INR) only on VM doses 1,4, and 8.

	• AE assessment • Administer SurVaxM in emulsion with Montanide plus sargramostim (local injection) or placebo (saline in emulsion with Montanide) plus saline (local injection) • Injection Site Assessment to evaluate for reaction • Tumor assessment by Brain MRI, assessed by the RANO criteria (-3 to -10 days from VM visit). **Telephone Follow up** 3 – 5 days after vaccine dose administration in Cycle 1 only to collect reaction data • Patient self-evaluates the injection site to evaluate for reaction and reports to research staff in telephone follow up.
Post Treatment Assessments	**End of Treatment Visit** will be performed 30 days after the last vaccine if the patient has not progressed, within 30 days of last MRI scan that confirms tumor progression or prior to the initiation of alternate treatment, whichever occurs first: • Full Physical Examination • Concomitant medication and treatment assessment • Laboratory Parameters o Immune profiling (PBMCs and ADA) • AE assessment • Tumor assessment by Brain MRI, assessed by RANO criteria, unless one was acquired in the previous 45 days. • Collect contact information for long-term follow-up **Long Term Follow-Up (LTFU) Assessments** will be performed every 8 weeks (± 2 weeks) from the End of Treatment visit. These can be conducted by telephone or in person. LTFU Assessments: • Patient Status Assessment • Concomitant medication and treatment assessment associated with cancer • Confirmation of continued contact information for long-term follow-up
Efficacy Endpoints:	Primary Endpoint: • OS is defined as the time from date of randomization to death due to any cause. Secondary Endpoint: • PFS is defined as the time from the date of randomization to the date of first observed disease progression or death due to any cause.

Statistical Analysis	Statistical Plan: This trial is designed as a parallel-groups, 3:2 randomized placebo-controlled trial of SurVaxM as add-on therapy to standard of care temozolomide for newly diagnosed glioblastoma. The primary endpoint is overall survival (OS) from time of randomization. The sample size will be n_1=159 in the SurVaxM arm and n_2=106 in the control arm for a total sample size of n_1+n_2=265. Hypothesis testing will be completed at a two-sided Type I error of 0.05. If OS is demonstrated to be statistically superior for SurVaxM over control, the study will be considered a success. All subjects meeting the eligibility criteria who signed a consent form and have been randomized to receive either SurVaxM or control will be considered evaluable for efficacy analysis. Safety analysis will be performed on all patients who have signed a consent form and received at least one dose of the study drug. The Intention to Treat (ITT) population will include all subjects randomized into the study. Subjects will be analyzed according to the treatment group to which they were randomized. Subjects will be followed for survival status after completion or discontinuation of the study drug and for progression or discontinuation of the study drug for other reasons. ***Sample Size Justification*** *Overall Survival* Assuming a 1-year survival rate of 75% in the SurVaxM group (Arm A; comparable to a median overall survival (mOS) of 29 months assuming an exponential distribution) and 60% in the control group (Arm B; comparable to a mOS of 16 months assuming an exponential distribution), 159 subjects will be randomized to SurVaxM and 106 subjects randomized to control. This analysis of the endpoint is event-driven and will complete when 142 deaths (combined across the 2 treatment groups) occur, assuming that the study had not been stopped earlier for efficacy or safety considerations, and assuming the study is not extended through the promising zone methodology. With 142 deaths, the study has approximately 90% power to detect a 44% reduction in the risk of death (HR = 0.56) in the SurVaxM group (versus control) with an overall 2-sided Type I error of 5%. Approximately 265 subjects will be randomized 3:2 between SurVaxM and control over an approximate 18-month period. Assuming uniform accrual over the 18-month period, exponential survival on both SurVaxM (1-year survival of 75%) and control (1-year survival of 60%), the targeted number of deaths is expected at month 35 (17 months after the last subject starts treatment). Deviations from this assumption are controlled by an event-driven approach: the final analysis will occur once the targeted number of deaths is accrued.

	Interim futility and efficacy analyses for OS are planned once 50% of the deaths (71 deaths) occur in the study. Information regarding the stopping rules for the interim analysis is provided in **Section 18.4.3**. ***Primary Efficacy Analyses*** *Overall Survival* The primary efficacy variable OS is defined as the number of days from randomization to death due to any cause. The primary analysis for OS will be based on the ITT population, according to the treatment group to which the subjects was randomized. Survival data will be analyzed by the Kaplan-Meier method, treating subjects with no observed death as censored at their last date known to be alive. A log-rank test stratified by KPS (70-80/90-100), MGMT status (methylated/unmethylated), and IDH-1 status (mutant/wild type) will be used as the primary analysis. Median survival will be estimated using the Kaplan-Meier method. Confidence intervals for median survival time will be calculated using the method of Brookmeyer and Crowley. The HR and 95% CI will be determined using a stratified Cox regression model, using the same strata as covariates, with Efron's likelihood approximation to account for ties in event times. Sensitivity analyses for the primary endpoint will be conducted using the Max-combo test as well as repeating analyses using the PP population.

Table of Contents

Table of Figures:

Table of Tables:

2 ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
APC	antigen presenting cell
AST	aspartate transaminase
CFR	code of federal regulations
CI	confidence interval
CP	conditional power
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DSC	dynamic susceptibility contrast
EC	Ethics Committee
eCRF	electronic case report form
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GBM	glioblastoma
Hgb	hemoglobin
HR	hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDH-1	isocitrate dehydrogenase 1
ITT	Intention to Treat
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IRB	Institutional Review Board
ITT	Intent to Treat
KLH	Keyhole limpet hemocyanin
LMW	low molecular weight
MGMT	O(6)-methylguanine-DNA methyltransferase
MHC	major histocompatibility complex
mOS	median overall survival
mPFS	median progression free survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
nGBM	newly diagnosed glioblastoma
OS	Overall Survival
PBMC	peripheral blood mononuclear cell

PD	progressive disease
PFS	progression free survival
PI	principal investigator
PsP	pseudoprogression
PH	proportional hazard
PHI	protected health information
PP	per protocol
PR	partial response
PWI	perfusion-weighted imaging
RANO	Response Assessment in Neuro-Oncology
SAE	serious adverse event
SD	stable disease
SOC	standard of care
TP	true progression
TME	tumor microenvironment
TMZ	temozolomide
ULN	upper limits of normal
VM	vaccine maintenance
VP	vaccine priming

3 BACKGROUND

3.1 Treatment of newly diagnosed glioblastoma (nGBM)

Glioblastoma is the most common primary malignant brain tumor in adults. In a randomized phase 3 multicenter trial, patients with newly diagnosed glioblastoma who received 60 Gy of radiation over 6 weeks with concurrent TMZ 75 mg/m^2 for 42 days, followed by adjuvant TMZ 150 mg to 200 mg/m^2 for 5 consecutive days each month for 6 months, the median overall survival for patients was 14.6 months compared to 12.1 months for patients in the control arm (1). In this study, the extent of prior surgical resection also affected overall survival. Patients who had surgical resection of their tumors (84%) had median overall survival of 15.8 months, whereas, those that had biopsy only (16%) had median overall survival of 9.4 months. To date, no other chemotherapeutic or biological agent has been proven to be more effective than TMZ for the treatment of newly diagnosed glioblastoma. One study demonstrated that the addition of bevacizumab to the Stupp regimen provided no added benefit to overall survival (2). Bevacizumab is approved by FDA for use in patients with glioblastoma based upon its ability to relieve neurologic symptoms and reduce the requirement for corticosteroid therapy.

3.2 Treatment on Trial

3.2.1 Composition of SurVaxM (SVN53-67/M57-KLH)

SurVaxM contains a synthetic peptide conjugate that stimulates immune responses capable of killing cancer cells that express the survivin molecule. Multiple copies of the modified peptide (SVN53-67/M57) are conjugated to Keyhole Limpet Hemocyanin (KLH) yielding a molecule designated as SVN53-67/M57-KLH. The SVN53-67/M57-KLH conjugate (SurVaxM) produces immune responses in mice and humans that are cross-reactive to the wild type survivin molecule expressed by tumor cells. The survivin peptide in SurVaxM is a defined antigenic peptide comprised of 15 amino acids that encompass multiple epitopes capable of binding human MHC class I and murine H2-Kb molecules. SurVaxM also contains a core antigenic epitope that has been modified by substitution of methionine for cysteine at amino acid position 57 (i.e., M57). This allows the core epitope in SurVaxM to be more immunogenic against survivin than the wild-type survivin epitope in humans with HLA-A*02 haplotypes (3). While SurVaxM is designed to bind HLA-A*02, computer algorithms predict, and clinical studies have shown, that its epitopes bind to other MHC class I molecules that are present in a large segment of the human population. Thus, SurVaxM is predicted to be effective at generating cytotoxic T lymphocytes (CTL) in a diverse group of patients with relatively limited HLA restriction.

SurVaxM is administered in emulsion with Montanide ISA 51, (Cross-Referenced Drug Master File 10870, Seppic, Inc. France). The emulsion is co-administered with a separate local injection of sargramostim (recombinant human GM-CSF; Leukine®) to facilitate attraction and maturation of local antigen presenting cells (APC) which ingest, process and present survivin peptide epitopes to the immune system. In the placebo control arm of this study, SurVaxM and sagramostim are replaced by saline.

3.2.1.1 Keyhole Limpet Hemocyanin (KLH)

The modified survivin peptide is chemically conjugated to Keyhole Limpet Hemocyanin. Two keyhole limpet hemocyanin genes (KLH1 and KLH2) encode protein monomers that oligomerize to form a large (20-monomer) protein with a molecular weight of about 390 kDa prior to

glycosylation. Each domain of a KLH subunit contains two copper atoms that together bind an oxygen molecule. KLH is available as a purified molecule derived from the Megathura crenulata mollusk maintained in aquaculture. KLH is a carrier molecule for vaccines. It generates a potent immune response and the abundance of lysine residues for chemical coupling of synthetic peptides allows a high ratio of survivin peptide molecules to KLH, increasing the likelihood of generating strong peptide-specific immune responses. In addition to survivin-specific antibodies, patients undergoing treatment with SurVaxM develop antibodies to KLH itself.

3.2.2 Montanide ISA 51

Montanide ISA 51 (Montanide) is an oil-based adjuvant product similar to Incomplete Freund's Adjuvant, which when mixed properly with a water-based solution in 1:1 w/w ratio, forms a water-in-oil emulsion. It consists of highly purified oil (Drakol VR), and a surfactant, mannide oleate. Montanide is manufactured by Seppic, Inc., and is provided in glass vials containing 3 mL of the adjuvant. Montanide is commonly used in human clinical vaccine protocols in the United States and is classified as an Investigational New Drug. Montanide acts to enhance immune responses to vaccines by an unknown mechanism. Peptide-based vaccines in emulsion with Montanide have been shown to induce T-cell responses against the immunizing peptides. Thus, the addition of Montanide ISA 51 to various antigens aids in the induction of both humoral and cellular immune responses. Toxicities most commonly observed include local pain, induration and erythema at injection sites.

3.2.3 Sargramostim

Sargramostim (Leukine®) is recombinant human granulocyte-macrophage colony stimulation factor (GM-CSF), a glycoprotein produced by recombinant DNA technology in a yeast expression system. Sargramostim has many actions, including stimulating proliferation and differentiation of hematopoietic progenitor cells. In the context of this trial, sargramostim serves as a local attractant and maturant for antigen presenting cells (APC) intended to facilitate presentation of SurVaxM to the immune system. The most common adverse reactions reported for systemically administered sargramostim are aching or pain in the extremities and joints, chills, headache, nausea, vomiting, abdominal pain and diarrhea. The subcutaneous dose used in this study is lower than that used for systemic administration and its action is thought to be predominantly local in close proximity to the site of vaccination with SurVaxM. The Physician Desk References and product package insert provide complete information on this drug.

3.2.4 Temozolomide (TMZ)

Temozolomide (TMZ) is an alkylating drug indicated for the treatment of patients with newly diagnosed glioblastoma. It is given concurrently with radiotherapy (chemoradiation) and then subsequently as adjuvant treatment for 6 or more cycles (5 daily doses every 28 days). The most common adverse effects (≥10% incidence) reported for TMZ include alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, incoordination, viral infection, amnesia, and insomnia. The most common Grade 3 to 4 hematologic laboratory abnormalities (≥10% incidence) that have developed during treatment with TMZ are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia. Allergic reactions have also been reported. The Full Prescribing Instructions provide complete information on this drug. All patients will receive adjuvant TMZ while enrolled on this study.

3.3 Immunologic effects of SurVaxM

3.3.1 Survivin-specific T cell responses to SurVaxM vaccination

Cellular proteins such as survivin are processed by the proteasome into individual epitopes that are presented by MHC class I molecules on the tumor cell surface where they are recognizable by specific effector cytotoxic T lymphocytes (CTL). The immune system of a cancer patient is often primed to recognize survivin epitopes and cancer patients frequently have circulating survivin-specific T cells that can be stimulated to proliferate by active vaccination against survivin (4, 5). Survivin-specific CTL kill tumor cells via engagement with MHC-I molecules on the surface of tumor cells that present survivin epitopes. In both phase I and phase II clinical studies of SurVaxM, vaccination produced specific anti-survivin CD8+ T cells reactive to multiple different epitopes contained within the immunizing survivin peptide. Multimers loaded with the survivin peptide epitopes contained in SurVaxM were used to test for T cell reactivity in the blood of patients in phase I and phase II studies **(Figure 1)**.

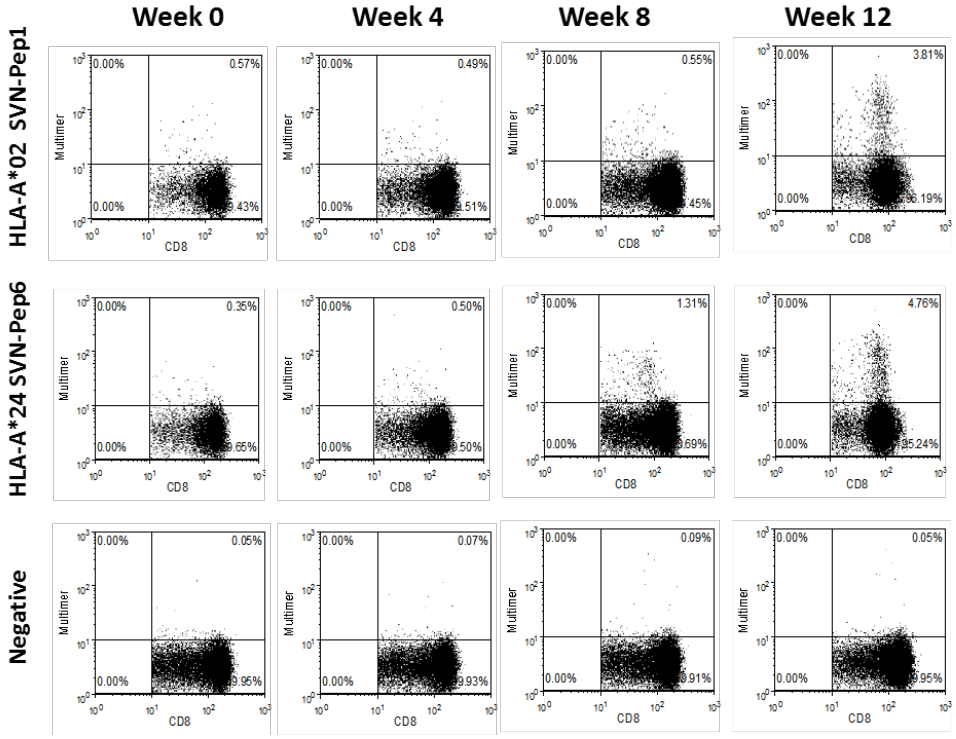

Figure 1: Multimer binding assay using phase I patient PBMC gated on CD8+ cells. HLA-A*02 and HLA-A*24 multimers detect increasing numbers of survivin-specific CD8+ T cells over the first 12 weeks of vaccination with SurVaxM by flow cytometry.

3.3.2 Stimulation of cytokine support by SurVaxM

To activate T-cell helper responses, antigens must be presented in conjunction with an MHC class II antigen (6). Once CD4+ cells have been activated by this mechanism, they proliferate and produce cytokines (e.g., IFN-α, IL-2, and IL-4) that enhance concomitant CD8+ antitumor immune response (7, 8). These cytokines are essential to provide a fully activated CD8+ antitumor CTL

response (9). MHC class II-restricted CD4+ T cells that are specific for tumor-associated antigens provide essential helper support to elicit and sustain cytotoxic CD8+ responses against tumor cells (10, 11). Vaccination with SurVaxM has been shown to produce cytokine support that may help to sustain CD8+ antitumor T cell responses (3).

3.3.3 Antibodies to SurVaxM

Although classically believed to reside and function within various intracellular compartments, survivin has more recently been identified on the plasma cell membrane of tumor cells, including glioblastoma (12). Therefore, cell-surface survivin is accessible to antibody-mediated antitumor responses and monoclonal antibodies to the modified survivin peptide contained in SurVaxM inhibit tumor growth *in vivo* (12). The precise mechanism by which antibodies to SurVaxM inhibit tumor growth is not currently known. As with survivin-specific T cells, anti-survivin antibodies are frequently detectable in the blood of cancer patients (13). In a phase I clinical study, vaccination with SurVaxM produced anti-survivin antibodies in most patients with recurrent malignant gliomas (14). Following serial vaccination with SurVaxM, most patients develop high titers of anti-survivin and anti-KLH IgG **(Figure 2)**.

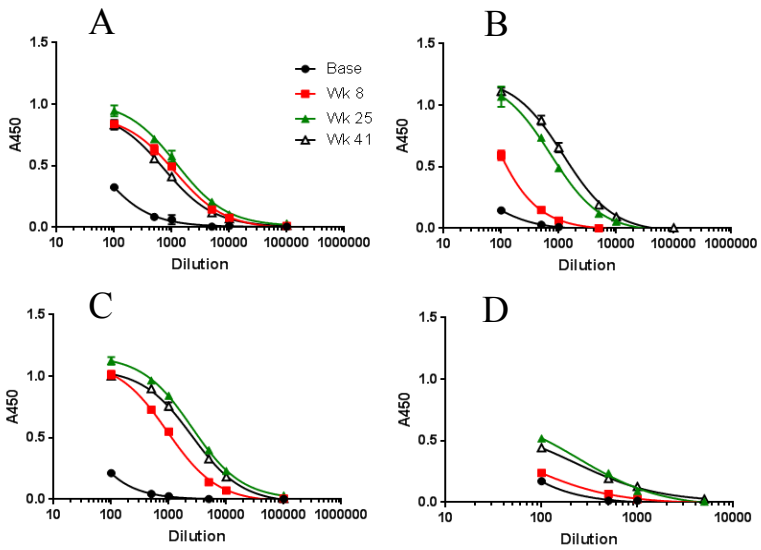

Figure 2: Survivin-specific IgG responses to SurVaxM in a representative phase II study patient. Antibodies to: (A) KLH, (B) SVN53-67/M57 peptide, (C) SurVaxM, and (D) scrambled (non-specific) peptide. Results at baseline (pre-immune) and 8, 25 and 41 weeks following first vaccination are shown. IgG for each was determined by ELISA using serial dilutions of patient sera.

3.4 Clinical Experience with SurVaxM

3.4.1 Results of a phase I clinical study of patients with recurrent malignant glioma

SurVaxM was initially studied clinically in a phase I trial conducted at a single institution (14). In that trial, nine patients with recurrent, survivin-positive malignant gliomas and either HLA-A*02 or HLA-A*03 haplotypes, and who had failed standard therapy, received SurVaxM (500 mcg) in Montanide ISA 51 with sargramostim (100 mcg) given subcutaneously at two-week intervals for four doses. Patients who survived six months or more without tumor progression, serious adverse events, or regimen-limiting toxicity were eligible to receive additional maintenance dosing every

three months thereafter. Toxicity attributable to SurVaxM was mostly limited to mild injection site reactions. The combination of SurVaxM in Montanide ISA 51 with sargramostim was well tolerated and the majority of adverse events (AE) were grade one. Six of nine patients experienced injection site reactions, all grade one, including localized areas of erythema related to vaccination. Three patients reported fatigue (grades 1 and 2), two patients experienced myalgias (grade 2). Lymphopenia was seen in 3 patients (all grade 1) and leukopenia (grades 1 and 2) occurred in three patients. The only grade 3 AE, a seizure, was not related to the vaccine. A single serious adverse event (SAE) consisting of renal failure occurred during the maintenance phase in one patient. This was proven by renal biopsy to be non-immunologically mediated and unrelated to the study drugs. Seven of eight evaluable patients survived longer than 12 months and two of these patients survived longer than 4 years. One patient had rapid tumor progression during the vaccine prime-boost phase and was not evaluable for clinical response.

3.4.2 Results of a single-arm phase II study of patients with newly diagnosed glioblastoma

A single-arm, multicenter, phase II trial was conducted in 63 patients with newly diagnosed glioblastoma with HLA-A*02, -A*03, -A*11 and -A*24 haplotypes and Karnofsky performance status ≥ 70 (15). All patients underwent craniotomy with gross total or near-total resection (≤1 cm^3 residual contrast enhancement) followed by chemoradiation (Stupp protocol). Thereafter, patients were treated with priming doses of SurVaxM (500 mcg) in emulsion with Montanide and sargramostim (100 mcg) every 2 weeks for 4 doses. This was followed by treatment with adjuvant temozolomide therapy and maintenance SurVaxM every 12 weeks until tumor progression. Immunogenicity of SurVaxM was assessed based on expansion of survivin-specific CD8+ T-cells and anti-survivin antibody (IgG) levels.

Patients ranged in age from 20-82 years (median = 60) with 38 males (60%) and 25 females (40%). Based on immunohistochemistry, survivin expression was detectable in 1-40% (median = 12%) of tumor cells. Measured from first dose of SurVaxM, median PFS was 13 months and median OS was 25.5 months **(Figure 3)**. The vaccine was immunogenic and produced survivin-specific antibody (IgG) titers and CD8+ T-cells detected using survivin multimers. The most common adverse events were localized injection site reactions with no serious adverse events attributable to the vaccine itself. Interim results of this single-arm phase II trial of SurVaxM/Montanide emulsion plus sargramostim indicate that 93% of patients survived greater than one year after diagnosis of glioblastoma.

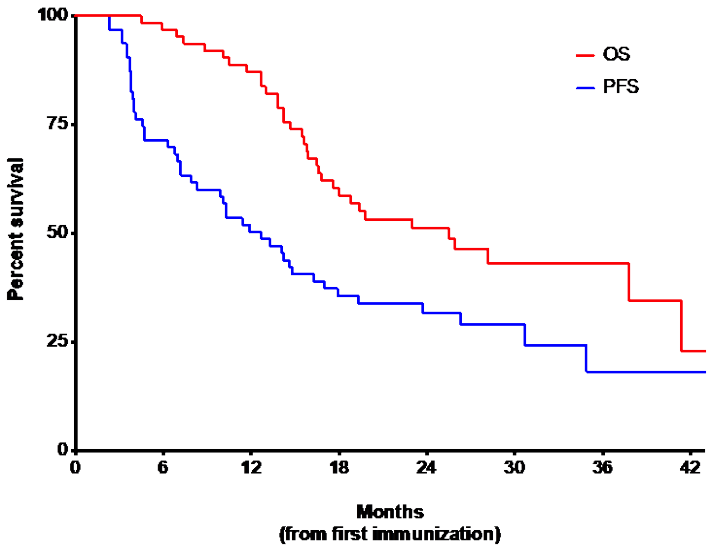

Figure 3: Progression-free survival (blue) and overall survival (red) in a single-arm phase II trial of 63 patients with newly diagnosed glioblastoma. Patients received SurVaxM in emulsion with Montanide plus sargramostim and adjuvant temozolomide post-surgery (≤1cm^3 residual enhancement) and chemoradiation therapy (Stupp protocol).

3.5 Safety Pharmacology of SurVaxM

Peptides that are administered in microgram quantities as vaccines do not follow standard pharmacokinetic models and such data are not likely to be useful in the ascertainment of vaccine safety. Previous studies of similar peptide designs have not shown any significant pharmacological effects upon vital functions. Consequently, pharmacological distribution studies of SurVaxM have not been performed.

Considering the route of administration (i.e., subcutaneous injection), it is very likely that SurVaxM in emulsion with Montanide will remain locally at the injection site for a long period and not be systemically available in any significant amount. Much of the peptide will be taken up by antigen presenting cells locally and then processed for presentation to the immune system. In addition, some fraction will be degraded locally by peptidases to produce clinically insignificant quantities of smaller peptides and individual amino acids. Therefore, as with many other peptide vaccines tested to date, SurVaxM is not expected to affect vital organ function directly. Nonetheless every effort has been made to address the safety of SurVaxM through pre-clinical animal toxicity studies.

In the study entitled “Subcutaneous Repeated Dose Toxicity Study of 012410-2 in C57BL/6 Mice with a Two-Week Recovery (Study No. 20003268)”, subcutaneous administration of SurVaxM at a dose of 500 mcg in adjuvant Montanide ISA 51 injected with murine GM-CSF every other week for 12 weeks was well tolerated by male and female mice throughout both dosing and recovery periods. Administration of SurVaxM did not cause mortality or signs of toxicity as evaluated by clinical or skin reaction observations, changes in body weights, ophthalmologic exams, necropsy observation, terminal body and organ weight measurement, clinical gross pathology and histopathological observations.

3.6 Pharmacokinetics of SurVaxM

Following subcutaneous injection of small quantities of conjugated peptide vaccines, the molecules are taken up and processed by antigen presenting cells (APC). Upon administration, biological peptides begin to be degraded into smaller peptide fragments and amino acids that are largely indistinguishable from those normally present in the systemic milieu. Consequently, in the doses utilized for vaccination, clearance of these molecules from the organism does not follow standard pharmacokinetic models. Absorption, distribution, metabolism and excretion of a peptide and its component amino acids cannot be confidently ascertained by standard methods. Thus, formal pharmacokinetic studies of SurVaxM have not been conducted in either animals or humans.

3.7 Study Rationale

3.7.1 Current therapy for glioblastoma

Glioblastoma is the most common malignant primary brain tumor of adults. Despite advances in surgery, radiation therapy and chemotherapy, it remains an incurable cancer. When using a widely accepted regimen of concurrent radiation and temozolomide (TMZ) followed by adjuvant TMZ alone (Stupp protocol) (Stupp 2005), the median overall survival of patients with newly diagnosed glioblastoma (nGBM) is 14.6 months (1). In one randomized study, the addition of tumor treating fields (TTF) to this regimen provided a median overall survival of 20.9 months compared to 16.0 months with the Stupp protocol alone (3). No other treatments have been proven to be better for nGBM than these.

3.7.2 Survivin in glioblastoma

Survivin is highly expressed during fetal development (16). Despite low-level expression in some normal adult tissues (17), major off-target toxicity of anti-survivin immunotherapy has not been observed (18). One study of gliomas of various grades showed that 29 of 29 glioma specimens (grades II-IV), but not normal brain tissue, contained survivin-positive cells. The mean percentage of cells detectable by immunohistochemical methods in each specimen was 70.0% in grade II (low grade) gliomas, 81.3% in grade III (anaplastic) gliomas and 85.0% in grade IV gliomas (glioblastoma) (19**)**. Therefore, survivin represents an important potential target for glioblastoma immunotherapy.

3.7.3 Immunosuppression by glioblastoma

Patients with glioblastoma have significant systemic immunosuppression as a result of various molecules produced by their tumors (20). Following tumor resection, immune function is at least partially restored. Surgical resection provides disease remission during which immunogens may be capable of stimulating more potent immune responses than at other points during the course of disease. This suggests that the optimal time to introduce immunotherapeutic vaccines may be during the interval following surgery when disease burden has been substantially reduced. Consequently, this study is being conducted with SurVaxM immunotherapy as an add-on to standard of care in patients with newly diagnosed glioblastoma (nGBM).

4 STUDY OBJECTIVES

4.1 Primary Objective

- To compare overall survival (OS) in patients with newly diagnosed glioblastoma between treatment arms A and B.

4.2 Secondary Objectives

- To tabulate the number and type of grade 3 and grade 4 toxicities, according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAEs) Version 5.
- To compare progression free survival in patients with newly diagnosed glioblastoma between treatment Arms A and B,
- To compare treatment-associated overall survival at pre-specified time points (OS-15, OS-18 and OS-24) between treatment Arms A and B.
- To compare treatment-associated progression-free survival at pre-specified time points (PFS-3, PFS-6 and PFS-12) between treatment arms A and B.

4.3 Exploratory and Scientific Objectives

- To evaluate the predictive value of perfusion-weighted imaging in assessing pseudo-progression and post-vaccination enhancement in patients receiving SurVaxM
- To evaluate the objective image-based tumor response rate (applicable only for patients with evaluable disease at study entry as defined by RANO criteria).
- To evaluate molecular predictors of response to SurVaxM, including MGMT methylation status, anti-survivin immunoglobin titers, survivin-specific CD8+ responses, tumor survivin expression levels and other molecular tumor tissue markers.

5 STUDY DESIGN

This is a prospective, randomized, placebo-controlled, multicenter study of patients with newly diagnosed glioblastoma (nGBM) to evaluate a peptide vaccine (SurVaxM) in emulsion with Montanide given together with locally administered sargramostim plus adjuvant oral temozolomide (Arm A) versus saline-Montanide emulsion with locally administered saline (instead of sargramostim) plus adjuvant oral temozolomide (Arm B).

Patients will be randomized 3:2 = A:B to treatment with SurVaxM in emulsion with Montanide plus sargramostim (local injection) ("SurVaxM/sargramostim") and standard-of-care TMZ (Arm A), or placebo (saline in emulsion with Montanide) plus saline (local injection)("Placebo/Placebo") and standard-of-care TMZ (Arm B). Randomization is described in Section 6.1. ***All patients in both Arms will receive the standard of care treatment with adjuvant TMZ.***

To be eligible to participate, patients must have undergone a contrast-enhanced, post-operative MRI scan within 72 hours of surgical resection documenting ≤1 cm^3 of residual contrast enhancement (gross-total or near-total resection). This must be followed by fractionated radiation therapy with concurrent temozolomide (chemoradiation) according to established Stupp protocol.

MRI must be performed following completion of chemoradiation to ensure no tumor recurrence or progression. All patients must undergo randomization within 16 weeks of surgical tumor resection in order to participate. Local neuroradiology reviews will be used for clinical decision making on the study. Central radiology reviews will be used for statistical determinations of PFS. See **Section 14.5** if pseudo-progression is suspected. All patients must undergo randomization within 16 weeks of surgical tumor resection in order to participate.

To participate, patients must meet the all inclusion criteria and no exclusion criteria as summarized in **Sections 7.3** and **Section 7.4** respectively and must sign an informed consent prior to undergoing any study-related tests or procedures.

In addition to the pre-treatment and post-treatment visits and assessments, there are three (3) treatment assessment phases for this trial:

- Vaccine Priming (VP) Phase
- Adjuvant Temozolomide (TMZ) Phase
- Vaccine Maintenance (VM) Phase

The TMZ treatment Phase may overlap both the VP and VM Phases as shown in **Figure 4**.

Once eligibility for the trial is determined, patients will be randomized as outlined in Section 4. As shown in **Figure 4**, study treatment is initiated with a 4-dose vaccine priming phase, followed by a vaccine maintenance phase. At least one "priming dose" must be administered in advance of initiating the standard of care adjuvant treatment with TMZ. TMZ should be started within 28 days (± 14 days) or as soon as feasible when residual effects from the chemoradiation are ≤ Grade 2 (up to 8 weeks also acceptable). Short delays due the COVID-19 public health emergency can be discussed with the Medical Monitor.

Figure 4: Drug Administration Schema

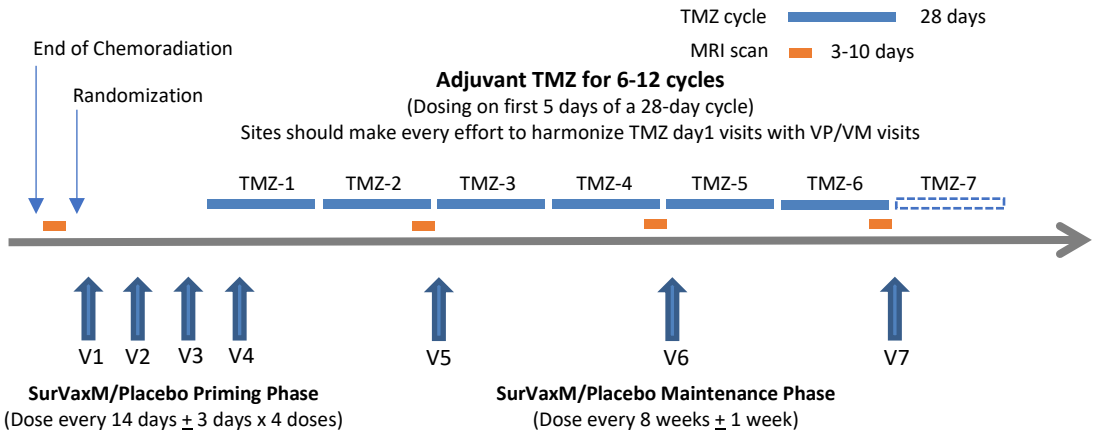

Figure 4: Treatment schema for Arm A (SurVaxM/sargramostim) and Arm B (Placebo/Placebo). Tumor assessment MRI scans are performed 2-10 days prior to administration of the next dose of vaccine/placebo and the initiation of every other corresponding TMZ cycle, as indicated.

The first (V1) priming dose of SurVaxM/sargramostim (or Placebo/Placebo) should occur within 7-28 days after completion of chemoradiation, unless the baseline MRI shows possible pseudo-progression (see **Section 14.5** if pseudo-progression is suspected). SurVaxM/sargramostim or Placebo/Placebo should be administered every 2 weeks (± 3 days) for a total of 4 doses during the priming phase and then every 8 weeks (± 1 week) during the maintenance phase. Following completion or discontinuation of TMZ, and in the absence of tumor progression, SurVaxM may still be continued every 8 weeks (± 1 week) during the maintenance phase until intolerance or disease progression.

At least one "priming dose" must be administered in advance of initiating standard of care adjuvant treatment with TMZ. Adjuvant TMZ should be started within 28 days (± 14 days) or as soon as feasible when residual effects from the chemoradiation are ≤ Grade 2 (up to 8 weeks also acceptable).

Adjuvant TMZ therapy should be given for at least 6 cycles (5 daily doses every 28 days) as tolerated, but not more than 12 cycles. Following completion or discontinuation of TMZ, and in the absence of tumor progression, SurVaxM may be continued every 8 weeks (± 1 week) during the maintenance phase until intolerance or disease progression.

This trial does not have any cross-over arm. Therefore, patients who experience tumor progression, or who come off the trial for any reason, are not eligible to receive continued treatment with the study drugs either under a compassionate exemption or via an expanded access protocol.

6 ASSIGNMENT TO TREATMENT

6.1 Randomization to study arms

Randomization will be in a 3:2 ratio to the investigational arm (Arm A) or to the placebo plus standard of care arm (Arm B) respectively. Three stratification criteria will be incorporated into randomization: MGMT methylation status (methylated or unmethylated), IDH-1 mutation (mutant or wild type), and KPS (70-80/90-100).

The Sponsor and all study staff will be blinded to the treatment arm, except one or more site pharmacists who will not participate in any other study activities.

6.2 Measures Taken to Minimize Bias (Blinding)

6.2.1 Vaccine Preparation by the Unblinded Pharmacist

Assignment of patients to Arms A and B will be decided on the basis of randomization and all assignments will be treated in a blinded manner. At each study site, a designated member(s) of the site's pharmacy staff with appropriate training and experience will function as the unblinded pharmacist(s) and will prepare all study vaccinations for Arms A and B. The unblinded pharmacist(s) will be responsible for preparing the injectable study medications for each patient in such a manner that investigators and staff remain blinded to the medication being administered. The unblinded pharmacist(s) will not convey any information about treatment assignment to patients or staff, except in a medical emergency where determination of treatment assignment is required for urgent therapeutic intervention. Unblinded pharmacist(s) will have no involvement in

the conduct of any other trial assessments or procedures. The pharmacists will be required to complete a Dosage Preparation Record to document the preparation process for each dose of study vaccination.

Following drug preparation, the visual appearance and physical handling characteristics of the injected drug preparations in Arms A and B are identical. Therefore, once prepared and released by the unblinded pharmacist for administration, there is no way for the patient, nor the administering health care professional to discern to which Arm the patient has been assigned.

6.2.2 Radiologic Assessment of Eligibility, Tumor Progression and Pseudo-progression

For the purpose of patient management and continuation on study, radiographic tumor progression will be determined by the local PI in collaboration with the local neuroradiologist using standardized response criteria (i.e., RANO). Neuroradiologists will be blinded to treatment arm assignment allocation and investigator assessments. For the purposes of statistical analysis of progression-free survival, MRI scans will be reviewed centrally by two neuroradiologists with adjudication of disagreements by a third neuroradiologist. The central neuroradiologists will provide no input to the local PI or local neuroradiologist concerning image interpretation or RANO determination.

6.3 Breaking of the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of patient safety. Whenever possible, the investigator should consult with the Study Medical Monitor before breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form.

Skin ulceration that is severe enough to require discontinuation of study treatment should not require unblinding since there is a very high probability that the skin condition will be due to Montanide, which is used in both treatment arms. In contrast, severe allergic reactions or anaphylaxis will require unblinding in most cases to ascertain if either the peptide-conjugate or sargramostim could be responsible for the adverse event.

7 PATIENT POPULATION

7.1 Number of Subjects

Approximately 265 eligible patients with newly diagnosed glioblastoma, will be enrolled over approximately 18 months. Up to 20 sites in the United States, Canada and China will participate and approximately 14-18 patients will be enrolled at each site.

7.2 Eligibility Considerations for Pre-Randomization Treatment and Imaging

7.2.1 Overview and Schema of Previous Treatment and Imaging Documentation

The pre-randomization treatment requirements are shown in **Figure 5**. All patients must undergo randomization within 16 weeks of surgical tumor resection in order to participate. Short delays due to COVID-19 public health emergencies should be discussed with the Medical Monitor to determine eligibility. The target population is patients with newly diagnosed glioblastoma who

undergo surgical resection. Within 72 hours following that surgical resection, patients must have undergone a contrast-enhanced MRI scan demonstrating ≤1 cm^3 of residual contrast enhancement (indicating gross-total or near-total resection). This must be followed by fractionated radiation therapy with concurrent temozolomide (chemoradiation) according to established Stupp protocol. MRI must be performed following completion of chemoradiation to ensure the absence of early tumor recurrence or progression and pseudo-progression (PsP).

Figure 5 Pre-Study Treatment and Imaging Requirements

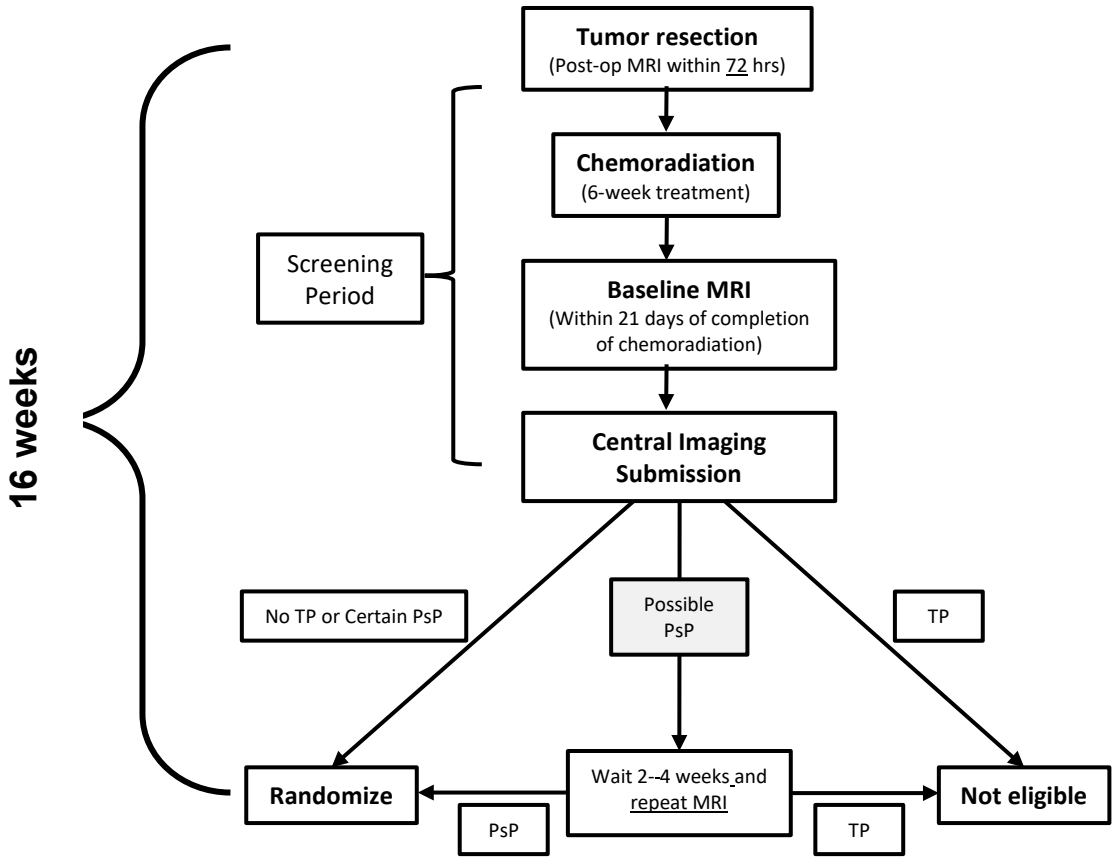

Figure 5: Pre-Study Treatment and Imaging Requirements

Screening assessments and baseline MRI are performed immediately after completion of chemoradiation and prior to randomization. Baseline MRI is used to confirm continued eligibility. PsP = pseudo-progression; TP = tumor progression.

7.2.2 Initial Eligibility Determination (the Post-op MRI Scan)

To be eligible for this study, patients must have undergone an MRI scan with and without gadolinium contrast completed within 72 hours following surgical tumor resection. This post-op scan does not have to have been performed at a participating center; however, it must be obtained

and reviewed by the PI or his/her designee at the enrolling center for initial eligibility determination. This post-operative scan must be provided to Central Imaging for review. Central Imaging will not provide input to the participating centers regarding eligibility determination. The scan must demonstrate ≤1 cubic cm of residual contrast enhancing tissue by volumetric analysis or ≤100 square mm on the section with the largest amount of residual enhancement. Patients who do not meet one of these two criteria on the post-operative scan are not eligible for participation in this study.

7.2.3 Determination of Continued Eligibility (the Baseline MRI Scan)

Following completion of chemoradiation, but prior to randomization, patients must undergo a baseline MRI scan performed at the enrolling center according to protocol criteria. **Baseline MRI scans must be performed at a qualified enrolling study site. Continued eligibility will be determined by the PI in collaboration with the local neuroradiologist.** Based on this scan, patients with early tumor progression will be declared not eligible for randomization or treatment on protocol. Patients determined to have pseudo-progression and meet all other eligibility criteria remain eligible for randomization and treatment on protocol. This Baseline MRI scan must also be provided to Central Imaging for review. Central Imaging will not provide input to the participating centers regarding eligibility determination.

7.2.4 Eligibility Considerations for Pseudo-progression

Since this is a study of patients with newly diagnosed glioblastoma treated with chemoradiation therapy and active immunotherapy, when new enhancement is seen on an MRI scan, every effort must be made to determine the presence of pseudo-progression and immune-based inflammatory changes and to distinguish these changes from true tumor progression. Approximately 25% of patients with glioblastoma who receive chemoradiation for newly diagnosed glioblastoma exhibit a transient increase in tumor enhancement that eventually subsides without change in therapy (pseudo-progression).

Patients with suspected, but not definitive, pseudo-progression, on the baseline MRI following chemoradiation may be imaged again at the enrolling institution within 2-4 weeks of the original baseline scan, at which time a final determination must be made regarding the presence of pseudo-progression (PsP) or true tumor progression (TP). Those patients determined to have pseudo-progression at baseline may proceed to randomization and treatment on protocol. The determination of pseudo-progression should be assisted by the use of perfusion-weighted imaging (PWI), specifically including dynamic susceptibility contrast (DSC) techniques.

Patients with increased or new gadolinium enhancement may continue on-study if the local neuroradiologist determines that the enhancement probably represents pseudo-progression (PsP), rather than tumor progression (TP). The use of dynamic susceptibility contrast (DSC) perfusion weighted imaging (PWI) should be used at this stage to aid in the determination.

7.3 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1 Age ≥ 18 years of age.

2 Have a Karnofsky performance status ≥ 70 (i.e., the patient must be able to care for him/herself with occasional help from others; refer to (**Appendix A**).

3 Pathologically confirmed diagnosis of glioblastoma of the cerebrum.

4 The result of tumor MGMT methylation study must be available.

5 The result of tumor IDH-1 mutation test must be available.

6 Have the following clinical laboratory values obtained within 14 days prior to registration:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelets≥ 100 x 10^9/L
- Hemoglobin (Hgb) > 9.0 g/dL
- Total bilirubin: ≤ 1.5 x ULN
- ALT and AST ≤ 4.0 x ULN
- Creatinine ≤ 1.8 mg/dL
- Prothrombin time (PT) within 1.5x normal limits
- Activated partial thromboplastin time (aPPT) within 1.5x control
- International Normalized Ration (INR) less than or equal to 1.4x control

7 Patients must have no active bleeding or pathological condition that carries a high risk of bleeding (e.g., coagulopathy)

8 Available results from a contrast-enhanced, post-operative Brain MRI completed within 72 hours following surgery documenting either: 1) gross total resection consisting of no gadolinium enhancement; or 2) near-total resection consisting of either ≤ 1 cm^3 nodular (i.e., volumetric) enhancement or ≤ 100 mm^2 in cross sectional area (i.e., linear enhancement).

Note: Patients who undergo either stereotactic biopsy or open biopsy for tissue diagnosis, or partial tumor resection, and who subsequently have a definitive surgical resection may still be eligible for inclusion, provided that the second procedure is performed within 14 days of the initial procedure and randomization can occur within 16 weeks of the date of surgical resection. In addition, to be eligible such patients must still meet post-operative imaging entry criteria as defined in item #8 above.

9 Patients must have completed initial radiation therapy with TMZ (chemoradiation) according to established Stupp protocol (Stupp 2005) for the treatment of their glioblastoma (i.e., completed a full course of fractionated radiation therapy and ≥ 75% of a course of concurrent TMZ chemotherapy).

10 Patients must be randomized within 16 weeks of surgical resection of their newly diagnosed glioblastoma.

11 No evidence of progressive disease at the post-chemoradiation timepoint (baseline evaluation), based on changes in the neurologic exam, corticosteroid use, or radiographic progression. See **Section 14.5** for suspected pseudo-progression.

12 Participants of child-bearing potential (not surgically sterile or post-menopausal) must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and have a negative pregnancy test prior to starting study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

13 Dexamethasone dose less than or equal to 4 mg daily at time of study enrollment. Every effort should be made to reduce the dose of corticosteroids to the absolute minimum dose required to control neurologic symptoms prior to receiving SurVaxM.

14 Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

7.4 Exclusion Criteria

Participants with any of the following will be excluded from this study:

1 Recurrent or progressive glioblastoma.

2 Gliosarcoma, anaplastic astrocytoma, oligodendroglioma, ependymoma, low grade glioma or any histology other than glioblastoma

3 Multicentric glioblastoma or glioblastoma involving the brainstem or cerebellum, or leptomeningeal or spinal extension present at diagnosis.

4 Residual contrast enhancement > 1 cm^3 on post-operative scan obtained within 72 hours following surgery.

5 Absence of MRI obtained within 72 hours of craniotomy documenting ≤ 1 cm^3 contrast-enhancing tumor.

6 Patients who elect to have Optune therapy (Tumor Treating Fields) are not eligible to participate.

7 Patient has had non-standard radiation therapy for glioblastoma (i.e., whole brain radiation therapy, gamma knife or LINAC stereotactic radiosurgery).

8 Prior or concurrent immunotherapy for brain tumor, including immune checkpoint inhibitors (pembrolizumab, nivolumab or ipilimumab) or other cancer vaccine therapy.

9 Prior or concurrent treatment with bevacizumab.

10 Patients with serious concurrent infection or medical illness, which in the treating physician's opinion would jeopardize the ability of the patient to receive the treatment outlined in this protocol with reasonable safety.

11 History of tuberculosis or other granulomatous disease.

12 Patient is pregnant or breast-feeding.

13 Patient has received any other chemotherapeutic agent or investigational drug in addition to standard of care radiation therapy with concomitant temozolomide (chemoradiation per Stupp protocol).

14 Patient with concurrent or prior malignancy is ineligible unless he or she has had curatively treated carcinoma-in-situ or basal cell carcinoma of the skin.

15 Patients who have had repeat craniotomy for tumor therapy after receiving RT and TMZ treatment.

16 Patients who have had surgical implantation of carmustine (Gliadel) wafers are not eligible to participate in this study.

17 Known history of systemic autoimmune disorder.

18 Known human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS) related illness or other serious medical illness.

19 Patient has a contraindication to MRI scans or to gadolinium contrast agent

20 Patient has a contraindication to temozolomide.

21 Patient is unwilling or unable to follow protocol requirements.

22 Patient has received an investigational treatment for the glioblastoma.

23 Any condition which in the Investigator's opinion makes the candidate unsuitable to receive the study drug or protocol procedures.

8 STUDY TREATMENT

Following randomization, treatment on-study will begin and will be administered in the outpatient setting. Patients will be randomized 3:2 to receive either SurVaxM in emulsion with Montanide plus sargramostim (Arm A) ("SurVaxM/sargramostim"), or saline in emulsion with Montanide plus saline (Arm B) ("Placebo/Placebo"). The Sponsor, patients and all study personnel, except the unblinded pharmacist(s), will be blinded to the treatment arm. The study drugs must be prepared at the approved clinical trial site by appropriately trained unblinded clinical pharmacy staff. Under no circumstance is either SurVaxM/sargramostim or Placebo/Placebo to be prepared or administered outside of a qualified study center pharmacy. Under no circumstance is either SurVaxM/sargramostim or Placebo/Placebo to be prepared by any of the blinded study staff at the institution.

8.1 Treatment Overview

There are three active treatment phases in this study:

- Vaccine priming (VP) phase,
- Adjuvant Temozolomide (TMZ) Phase
- Vaccine Maintenance (VM) Phase

The TMZ treatment Phase may overlap both the VP and VM Phases as shown in **Figure 4.**

In the VP phase, four (4) doses of active drug SurVaxM/sargramostim (Arm A) or Placebo/Placebo (Arm B) will be administered every 2 weeks (± 3 days) and are designated as V1, V2, V3 and V4 in **Figure 4**. V1 must be administered within 7 – 28 days after completion of chemoradiation unless pseudo-progression is suspected. See **Section 14.5** if pseudo-progression is a consideration, for requirements for follow-up MRI scans.

At least one "priming dose" (V1) must be administered in advance of initiating the standard of care adjuvant treatment with TMZ (TMZ Phase). Adjuvant TMZ should be started within 28 days (± 14 days) of completion of chemoradiation, or as soon as feasible when residual effects from the chemoradiation are ≤ Grade 2 (up to 8 weeks also acceptable). In the TMZ phase, all patients will receive TMZ, consisting of 5 sequential daily doses self-administered during the first 5 consecutive days of every 28 days. This 28-day period is defined as a TMZ cycle. If feasible, the initiation of TMZ should be aligned with one of the vaccine priming or vaccine maintenance doses; however, the initiation of adjuvant TMZ should not be significantly withheld when patient becomes eligible. Within the assigned visit windows, over time the TMZ visits should be aligned with VM visits for patient convenience if possible. TMZ dosing may overlap with the VP phase and will overlap with the VM phase. TMZ treatment should be given for at least 6 cycles, if it is tolerated, but not more than 12 cycles.

After the VP phase is complete, patients will start the vaccine maintenance (VM) phase, whether or not the TMZ phase has been initiated. Any MRIs that may be obtained in the time interval between the last VP dose and the first on-study MRI for the VM phase should be collected. In the VM phase, patients will receive additional vaccinations of SurVaxM/sargramostim or Placebo/Placebo, designated in **Figure 4** as sequentially numbered vaccinations (V5, V6, etc.), after every two TMZ cycles (approximately every 8 weeks (±1 week). SurVaxM/sargramostim or Placebo/Placebo will be administered every 8 weeks (±1 week) until tumor progression or for a maximum of 24 months, irrespective of whether treatment with adjuvant TMZ is ongoing.

Patients must undergo vaccine administration, all MRI scans (except for the 72-hour post-operative scan) and all disease assessments at their enrollment site or at another approved site that is participating in this trial. Transfer of patient care to another study site must be discussed with the Medical Monitor.

8.2 Study Drug Administration

8.2.1 Arm A (SurVaxM/sagramostim plus temozolomide) in VP and VM Phases

Patients randomized to Arm A will receive SurVaxM/sargramostim in combination with adjuvant temozolomide (TMZ) according to the VP, TMZ, VM schedule described in **Section 8.2**.

Patients will receive 500 mcg SurVaxM (0.5 mL) in 50/50 volume emulsion with Montanide ISA 51 (0.5 mL), prepared by the unblinded pharmacist as outlined in the Pharmacy Manual. A second separate injection of 100 mcg sargramostim in sterile water or bacteriostatic water (0.4 mL) will be prepared by the blinded pharmacist as outlined in the Pharmacy Manual and administered in close proximity (1-3 cm) to the first injection.

Subcutaneous injections of SurVaxM in emulsion with Montanide must be performed using an appropriate needle (a 22- or 23-gauge needle is strongly recommended). Each dose of SurVaxM vaccine in emulsion with Montanide will be given in a total volume of 1 mL. Immediately following the SurVaxM injection, 100 mcg sargramostim (0.4 ml of a 250 mcg/mL solution) will be administered subcutaneously as a second separate injection given in close proximity (1-3 cm) to the SurVaxM/Montanide injection. The time and location of each injection will be recorded. In both the VP Phase and VM phase, the subcutaneous injections should alternate between left and

right deltoid sites and as outlined in **Section 8.4**. Any injection site reaction should be assessed according to the instructions in **Section 15.5.5.**

8.2.2 Arm B (Placebo plus temozolomide) in VP and VM Phases

Patients randomized to Arm B will receive the placebo (saline) (0.5 mL) in emulsion with Montanide ISA 51 (0.5 mL). Immediately following the saline-Montanide injection, a second separate injection of placebo (saline) (0.4 mL) will be injected within 1-3 cm of the first injection site. All patients in Arm B will also receive adjuvant temozolomide (TMZ) according to the VP, TMZ, VM schedules described in **Section 8.2**. The placebo saline (0.5 mL) in 50/50 volume emulsion with Montanide ISA 51 (0.5 mL) and the second separate injection of saline (0.4 mL) will be prepared by the blinded pharmacist as outlined in the Pharmacy Manual.

Injections of saline in emulsion with Montanide must be performed using an appropriate needle (a 22- or 23-gauge needle is strongly recommended). Each dose of saline in emulsion with Montanide will be given in a total volume of 1 mL (0.5 mL saline and 0.5 mL Montanide). The time and location of each injection will be recorded. In both the VP Phase and VM phase, the subcutaneous injections should alternate between left and right deltoid sites and as outlined in **Section 8.4**. Any injection site reaction should be assessed according to the instructions in **Section 15.5.5.**

8.3 All Patients: Adjuvant Temozolomide (TMZ Phase)

In all patients, adjuvant TMZ should be started within 28 days (±14 days) of completion of chemoradiation, or as soon as feasible when residual effects from the chemoradiation are ≤ Grade 2 (up to 8 weeks also acceptable). All patients will receive SOC temozolomide in 28-day cycles (i.e., 1 daily dose of temozolomide for 5 consecutive days beginning every 28 days). This is defined as a temozolomide cycle (TMZ Cycle). TMZ will be self-administered orally around the same time each day on days 1 through 5 of each 28-day cycle. Each 28-day period is considered one TMZ cycle. As per standard of care, adjuvant TMZ should be given for at least 6 cycles (5 daily doses every 28 days) if it is tolerated, but not more than 12 cycles in total.

All patients will begin treatment with concurrent oral TMZ according to the schedules described in **Section 8.3**. TMZ is dosed on the first five (5) consecutive days of a 28-day schedule.

In the first TMZ cycle, oral TMZ should be taken at a dose of 150 mg/m^2 body surface area (BSA) per day for 5 consecutive days in the first TMZ cycle. Dosing should occur according to instructions on the product label and per standard practice, subject to the Dose Adjustment guidance outlined in **Section 8.4.2**. If tolerated, the dose will increase to 200 mg/m^2 body surface area per day in subsequent TMZ cycles or modified according to **Section 8.4.2**. Any change in weight of more than 10% will require re-calculation of the administered TMZ dose; otherwise, dosing may be based on the baseline weight. The total dose of TMZ will be rounded to the nearest 10 mg increment. TMZ should continue for at least six cycles up to a maximum of 12 cycles, unless intolerance or tumor progression occurs.

8.4 Dosing Considerations

8.4.1 Selection of injection sites for dosing of SurVaxM or placebo

Injections over the deltoid muscle are strongly preferred and the site of administration should alternate between left and right arms between successive treatments. Alternative sites, including the anterior thigh or abdomen, may be used if necessary, but are not preferred. If possible, injections should not be given in areas of skin with active dermatologic conditions (such as persistent injection site reactions, infection, edema, or scarring) since such sites might not provide normal local immunologic responses or accurate evaluation of localized adverse events. Extremities with previous proximal lymph node excision or dissection (e.g., axilla or groin) should not be used for injections. In such patients, alternative sites should be used. If conditions contraindicate recommended deltoid injection sites for an individual patient, as outlined here, the plan for injection should be discussed with the Medical Monitor. Following administration of each dose of SurVaxM or placebo, patients must remain in clinic for observation for a minimum of 30 minutes to detect and treat any potential immediate hypersensitivity (allergic) reactions.

8.4.2 SurVaxM Dose Omission and Discontinuation for Toxicity

Since toxicities related to SurVaxM are expected to be immunologically mediated, rather than dose-dependent, no adjustment to the administered dose will be allowed. If any significant unexpected toxicity (e.g., CTCAEv5 Grade 3 or greater) is observed, and there is a reasonable likelihood that the event may be associated with administration of SurVaxM, Montanide or sargramostim, the next immunization for that patient should be withheld until the toxicity improves to mild severity or less. If significant toxicity is observed again or is not reversible by the time of the next scheduled dose, all further immunizations should be discontinued, and the Medical Monitor should be consulted.

Administration of SurVaxM should be discontinued if it causes:

Severe hypersensitivity (i.e. systemic allergic) reaction that leads to any of the following:

i. Hypotension requiring blood pressure support with intravenous fluids or medications (pressors)
ii. Admission to the hospital
iii. Intubation to protect airway
iv. Angioedema involving the face, oropharynx, larynx or trachea
v. Cardiac arrest or arrhythmia
vi. Any other associated medical condition that in the judgment of the PI would preclude further safe administration of the drug

8.4.3 Dose Adjustments

8.4.3.1 Dose Adjustments of Temozolomide (TMZ)

A dose of 150 mg/m² body surface area per day (**Table 1**; Dose Level 1) will be used initially and in subsequent TMZ cycles pending hematologic count recovery. Any change in weight of more than 10% will require re-calculation of the administered TMZ dose; otherwise, dosing may be based on the baseline weight. The total dose of TMZ shall be rounded to the nearest 10 mg

increment. Dosing should occur according to instructions on the product label and per standard practice, with consideration to the guidance outlined here (see **Table 1 and Table 2**).

Table 1 Temozolomide Dose Levels for Maintenance Treatment

Dose	Level Dose (mg/m2/day)	Remarks
-1	100 †	Reduction for prior toxicity
1	150	Dose during Cycle 1
2	200	Dose during Cycles ≥ 2 in absence of Grade 3 or higher toxicity

†TMZ is to be discontinued if dose reduction to less than 100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction. TMZ=temozolomide; CTC=Common Toxicity Criteria.

Table 2 Temozolomide Dose Reduction Guidelines

Toxicity * Discontinue TMZ	Reduce TMZ by 1 Dose Level	Discontinue TMZ
Absolute Neutrophil Count	less than 1.0 x 10^9/L	See footnote†
Platelet Count	less than 50 x 10^9/L	See footnote†
CTC Non-Hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4†

*TMZ dose levels are listed in **Table 1**.
†TMZ is to be discontinued if dose reduction to less than 100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction. TMZ=temozolomide; CTC=Common Toxicity Criteria.

TMZ dose adjustments should be prescribed as clinically appropriate, at the Investigator's discretion with consideration to the product label recommendations (which may be more conservative than the guidance provided here).

Initiation of TMZ should not begin until the patient's peripheral blood counts have recovered from chemoradiation such that absolute neutrophil count (ANC) is ≥ 1500/µL and platelet count is ≥ 100,000/µL (see †**TMZ** is to be discontinued if dose reduction to less than 100 mg/m2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction. TMZ=temozolomide; CTC=Common Toxicity Criteria.

Table 2). Delays in the initiation of TMZ will be recorded in the eCRF.

During TMZ cycles, up to a three-week dose delay in TMZ administration may be considered until the patient's blood count returns to an acceptable level (ANC ≥ 1500/µL and platelet count ≥ 100,000/µL).

TMZ dosing should continue for at least six cycles (at the discretion of the investigator) up to a maximum of 12 cycles, unless intolerance or tumor progression occurs.

Deviations from the above-outlined treatment schedule are allowed and will not represent protocol violations, when appropriate as per standard of care. However, such deviations must be discussed with the Medical Monitor in advance to ensure appropriate visit scheduling.

If temozolomide is discontinued for any reason other than tumor progression, SurVaxM/placebo treatment may continue at the Investigator's discretion.

Every effort should be made to administer all trial treatments on the planned schedule. In the event that individual patients experience treatment related toxicity, subsequent trial treatment may be delayed, omitted or discontinued as described below.

8.5 Study Timeline

Patients on-study will receive treatment until disease progression, unacceptable toxicity, voluntary withdrawal or death. All enrolled subjects will be followed until death to determine overall survival (primary endpoint).

9 CONCOMITTANT SURGERY, MEDICATIONS, OTHER VACCINATIONS AND SUPPORTIVE CARE

9.1 Neurosurgical intervention for new contrast enhancement while on-study

Patients who undergo re-biopsy or surgical re-resection of intra-cranial tissue, and who are subsequently found to have no pathologic evidence of persistent or recurrent tumor in the surgical specimen whatsoever may, upon consultation with the Medical Monitor, be eligible to continue to receive treatment on-study with follow-up to document continued progression-free survival.

9.2 Corticosteroids and immunosuppressive medications

Patients with brain tumors frequently are placed on high potency corticosteroids for peri-operative management of brain swelling and also during radiation therapy. Every effort should be made to reduce or eliminate corticosteroid use before treatment on-study with SurVaxM. If possible, corticosteroids should be discontinued prior to initial vaccination (V1) or as soon as feasible following completion of chemoradiation.

The use of all standard supportive medication is permitted, although concurrent treatment with immunosuppressive or immunomodulatory agents is strongly discouraged. Concomitant systemic corticosteroids are to be avoided if at all possible. If used, doses of corticosteroids should be the absolute minimum necessary for appropriate clinical management. If any new or increased dose of corticosteroids is necessary due to neurologic signs or symptoms, a rigorous evaluation for recurrent glioblastoma should be conducted and, in the absence of progressive disease, every reasonable effort should be made to taper the patient from corticosteroids as quickly as clinically feasible.

9.3 Other cancer therapies

Patients must not receive additional investigational agents or anti-cancer therapies, unless progression of disease warrants discontinuation of study treatment and commencement of alternate therapies. Patients who begin new anti-cancer therapy, including investigational therapy, chemotherapy, cytokine therapy, immunotherapy (including other cancer vaccines and immune

checkpoint inhibitors) must discontinue SurVaxM treatment, and will be followed for overall survival.

Administration of SurVaxM should be discontinued in patients who develop an unrelated non-CNS malignancy other than basal cell carcinoma of the skin while on this protocol. Such patients should still be followed for progression-free survival and overall survival.

9.4 Nausea and emesis

Patients that receive temozolomide may experience nausea and emesis. Participants may be pre-treated for nausea and vomiting with anti-emetics according to institutional standard of care as deemed appropriate by their study physician.

9.5 Vaccination for infectious diseases (including SARS-CoV-2)

Participants may receive routine vaccinations (must be attenuated) for infectious diseases, including, but not limited to SARS-CoV-2, tetanus, influenza, pneumococcal pneumonia, hepatitis, and herpes zoster (shingles) as deemed necessary or appropriate by their study physician.

Vaccination for prevention of SARS-CoV-2 (COVID-19) should be administered during the maintenance phase as close to the midway point between SurVaxM doses as possible. If a second dose of the SARS-CoV-2 vaccine is required, the next dose of SurVaxM should be delayed for 4-6 weeks.

9.6 Elective non-neurological surgery

Participants may undergo elective surgery, other than for re-resection of their tumor due to tumor progression, during the maintenance phase of the study, as determined to be appropriate or necessary by their treating physician(s). Procedures should be conducted according to institutional standard of care. Treatment may then continue on schedule without removal from the study. Reasonable effort should be made to defer planned elective surgery to a point during the maintenance phase to a point midway between 8-week SurVaxM doses. In making a decision to perform non-urgent or elective surgery on patients, it should be kept in mind that the potential effects of anti-survivin vaccination on wound healing have not been studied. In addition, the effect of temozolomide on platelet and WBC counts should be taken into account in accordance with standard medical practice and managed accordingly.

9.7 Pneumocystis prophylaxis

Antibiotic prophylaxis with trimethoprim and sulfamethoxazole or other agents for prevention of pneumocystis carinii pneumonia (PCP) for the management of glioblastoma patients receiving TMZ is permitted according to the local investigator's clinical judgment and institutional standard of care.

9.8 Other medications

Medications for seizures, hypertension, hyperlipidemia, diabetes mellitus and other significant medical conditions should be used as clinically indicated for the patient's individual condition according to standard medical practice and institutional standard of care.

9.9 Medication documentation

All concomitant medication taken within 30 days prior to the VP phase through (whichever occurs first) either: 1) 30 calendar days after the last on-study MRI scan or, 2) initiation of alternate anticancer therapy will be documented in the eCRF. All concomitant medications required to treat study-drug related toxicity should be reported regardless of the timeframe relative to study drug dosing. All anti-cancer treatments taken throughout the duration of study follow-up should also be recorded in the eCRF.

10 GUIDANCE FOR MANAGEMENT OF EXPECTED TOXICITY

10.1 Local Injection Site Reactions

In previous studies of SurVaxM, local injection site reactions were the most common associated adverse events. However, not all patients will experience an injection site reaction with the first few doses of vaccine. In addition, not all patients who experience an injection site reaction will experience a reaction with subsequent injections of vaccine. Erythema and pruritus occurred most frequently, but localized swelling, pain, rash, induration, bruising and urticaria are also relatively common. Some injection site reactions may extend for several centimeters into the surrounding dermis and can take several days to resolve.

More serious skin conditions such as epidermal ulceration and granulomatous panniculitis are also possible. Skin ulcerations can become secondarily infected and may require antibiotic therapy. Severe skin reactions are most likely attributable to Montanide ISA 51 and may be more common with injections that are too superficial or with emulsions that are not thoroughly mixed. Severe skin reactions involving ulceration should be discussed with the Medical Monitor.

Clinical experience to date suggests that nearly all injection site reactions are tolerable and resolve without the need for intervention. Topical corticosteroids are permitted to treat injection site reactions at the discretion of the investigator, but their use is discouraged if not absolutely necessary. Systemic and intra-lesional corticosteroid therapies should be reserved for rare severe injection site reactions (e.g., granulomatous panniculitis) since they may compromise the desired immune response to the vaccine and could potentially negate its anti-tumor effects. Topical or systemic non-steroidal anti-inflammatory agents (e.g., ibuprofen, naproxen, aspirin) or antihistamines (e.g., loratadine, fexofenadine, and diphenhydramine) may be used as alternatives; however, routine use to prevent injection site reactions should be avoided, and doses should be the minimum necessary for appropriate clinical management.

10.2 Severe Skin Reactions.

Rarely, necrotizing granulomatous panniculitis with scarring and possible skin ulceration may occur as a result of subcutaneous injection of vaccines containing Montanide ISA 51. In such lesions, induration and deep nodularity can occur at injection sites. High frequency ultrasound may be used to evaluate the injection sites of patients who complain of persistent tenderness or induration lasting over 4 weeks after injection to aid in this diagnosis. If panniculitis is superficial, it may affect the vascular supply to the epidermis leading to superficial skin ulceration. The risk of this complication may be minimized by ensuring that vaccine injection is not given too superficially and that mixing of the emulsion is done correctly (see **Pharmacy Manual**).

10.2.1 Treating Severe Injection Site Reactions.

Severe injection site reactions are uncommon. Patients that experience skin necrosis or ulceration may be treated with intralesional injection of Kenalog (1 ml of 5 mg/ml solution) at the vaccine injection site approximately 4 weeks after vaccination. It is recommended that the injection site be re-assessed 4 weeks after Kenalog administration and further doses be modified based on clinically determined response. It is possible that intralesional Kenalog could attenuate the desired immunological response to vaccination. If skin ulceration occurs, secondary cellulitis in the area of ulceration is possible. In such cases, microbial culture and appropriate antibiotic therapy may be indicated. Very rarely, surgical management of ulcerative skin lesions could be required.

10.2.2 Grading of Injection Site Reactions.

SurVaxM injection sites should be rotated in accordance with the applicable study guidelines **(Section 8.4).** Injections should not be given to areas with evidence of significant persistent local reaction. Injection site reactions are considered adverse events and should be reported as such, using an appropriate descriptive term. For example, "injection site erythema", or "injection site induration" should be used rather than the less descriptive term "injection site reaction". Injection site reactions should be assessed as outlined in **Section 15.5.5**.

10.3 Hypersensitivity Reactions

Hypersensitivity reactions in response to SurVaxM vaccination could occur. Precautions should be taken to prepare for the possibility of hypersensitivity or anaphylactic reactions after SurVaxM administration. Patients should be observed according to institutional standards, but for a minimum of 30 minutes following each vaccination to evaluate and treat any potential immediate hypersensitivity reactions. **Note:** Severe hypersensitivity reactions that are attributable to SurVaxM may require discontinuation of the drug (see **Section 8.4.3**).

The use of routine supportive medication is permitted for hypersensitivity reactions, although routine use of "prophylactic" antihistamines, nonsteroidal anti-inflammatory agents and topical or systemic corticosteroids in the absence of significant documented hypersensitivity should be avoided. If used, doses of corticosteroids should be the minimum necessary for appropriate clinical management. If any new administration of, or increased dose of, systemic corticosteroids is necessary, every effort should be taken to taper, and preferably discontinue treatment with them as quickly as is clinically feasible.

For fever or injection site pain, acetaminophen (325 mg tabs, 1 or 2 orally every 4 hours as needed) should be utilized preferentially. Pre-treatment of participants with acetaminophen may be instituted as warranted for an oral temperature of 38°C or higher or a forehead (skin) temperature of 37.5°C or higher. Patients with fever lasting more than 8 hours after treatment should be evaluated for potential infection. Aspirin, naproxen and ibuprofen are acceptable alternatives to acetaminophen for pain or fever, but they are not preferred.

For mild to moderate local injection site pain that is unresponsive to acetaminophen, oral opiates may be used (e.g., oxycodone, 5–10 mg orally every 4 hours, as needed). Pain that is of more than mild to moderate grade should be investigated for sources other than the therapy and managed accordingly.

For delayed hypersensitivity reactions, investigators should treat for symptomatic relief but avoid corticosteroid use whenever possible.

10.4 Rashes and Skin Conditions Not in Proximity to the Injection Site

Investigators should treat for symptomatic relief but should avoid systemic corticosteroid use if possible. Alternatively, antihistamines and topical corticosteroids should be considered for this indication.

11 TREATMENT DURATION AND DISCONTINUATION

11.1 Duration of Treatment

Provided that there is no tumor progression or unacceptable toxicity, treatment with adjuvant temozolomide should continue for at least 6 cycles, but not longer than 12 cycles. After discontinuation of temozolomide, participants may remain on study and continue to receive treatment with SurVaxM in emulsion with Montanide plus sargramostim (Arm A) or placebo (Arm B) up to a maximum of 24 months following randomization Treatment should continue on-study in the absence of any of the following: disease progression, unacceptable toxicity, inter-current illness that prevents further administration of treatment, inability or refusal to comply with medication regimen, outpatient imaging, or clinic visit regime, or if the participant withdraws from the study. This trial does not have a cross-over arm. Therefore, patients who experience tumor progression, or who come off the trial for any reason, are not eligible to receive continued treatment with the study drugs either under a compassionate exemption or via an expanded access protocol.

11.2 Duration of Follow-Up

All patients treated on study will be followed for survival status until death or loss to follow-up.

11.3 Completion of Study

All patients will be followed until death, discontinuation from study follow-up, or termination/completion of the study. Patients who die or complete the study follow-up through study closure will be considered to have “completed” the study.

The study will be declared complete when sufficient data is obtained to conclude the study. It is anticipated that the enrollment period will be 18 months, and follow-up will continue for 18 months after enrollment of the last patient. Therefore, the study duration is expected to be up to 36 months.

Termination of this study may occur at any time because of a regulatory authority decision, drug safety problems, or at the discretion of the Sponsor or MimiVax, LLC. In addition, MimiVax and the Sponsor jointly retain the right to discontinue development of SurVaxM at any time. If a study is prematurely terminated or discontinued, the Sponsor will notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a period of time to be determined by the Sponsor. All study materials must be collected, and all case report forms (CRFs) must be completed to the extent possible.

12 TREATMENTS AND ASSESSMENTS

Informed consent ***MUST*** be completed prior to receiving any study related procedures. Eligibility of each participant must be established prior to randomization, including the determination of continuing eligibility based on the baseline MRI scan(s) following chemoradiation.

12.1 Schedule of Investigations, Data Collection and Deviations

The study is divided into phases with associated evaluations and procedures that must be performed at specific time points, as described in the following sections. The Schedule of Procedures and Observations (**Appendix C**) provides a tabular summary of the frequency and timing of various treatments, laboratory and imaging measurements and safety assessments.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances that are outside of the control of the investigator that may make it not feasible to perform the test. In these instances, the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the study investigator will document the reason for this and any corrective and preventive actions that have been taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

12.2 Screening Period

Prior to the performance of any study-specific procedures, the nature of the study will be explained to the patient and he/she will be asked to give written informed consent. Informed consent must be obtained prior to any study-specific procedures that are not part of the patient's normal care. However, assessments that are performed according to standard-of-care procedures prior to receipt of informed consent may be utilized to fulfill the screening requirements.

The assessments outlined for the Screening Visit in the study Schedule of Procedures and Observations (**Appendix C**) will be completed for each patient prior to inclusion in the study, and results will be evaluated to verify entry criteria prior to study entry.

12.3 Treatment Period

Following randomization, patients should begin protocol treatment as soon as feasible. The patient should begin protocol treatment within 7-28 days following completion of chemoradiation, although this time may be extended if pseudo-progression (PsP) is suspected (see **Figure 5** for details). The study Medical Monitor or his/her designee should be contacted for any extenuating circumstances that could prevent timely initiation of protocol treatment. Adjuvant chemotherapy with temozolomide should not begin for 4 weeks following completion of chemoradiation. Specific procedures to be performed during the VP and VM treatment phases are outlined in the Schedule of Procedures and Observations (**Appendix C**).

12.4 Treatment Completion/Discontinuation and End-of-Treatment Visit

The End-of-Treatment (EOT) visit should be performed within 30 days of last study MRI scan completion that confirms tumor progression or prior to initiation of alternate therapies (whichever occurs sooner). Follow-up and documentation of adverse events and concomitant medications should continue for one month following the date of tumor progression. Specific procedures to be

performed at the End-of-Treatment visit are illustrated in the Schedule of Procedures and Observations (**Appendix C**)

12.5 Post-Treatment Follow-up Phase

Patients who discontinue study treatment will be followed for overall survival with visits or phone contact every 8 weeks (± 2 weeks) until death or lost to follow-up. Information on subsequent cancer treatments should also be collected. It is critically essential to the study goals that every reasonable effort be made to ascertain and record the date of death for all patients that are taken off-study.

13 STUDY OR STUDY SITE TERMINATION AND PATIENT DISCONTINUATION

13.1 Study or Study Site Termination

If the Investigator, the Sponsor or Sponsor's Designee or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, and Study Monitor. Conditions that may warrant termination of the study or discontinuation of a study site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at a rate commensurate with good clinical research practice and acceptable to the Sponsor
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonisation (ICH) sixth efficacy publication (E6) on Good Clinical Practice, section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21, with appropriate notification of the FDA and all IRB's having approved the study protocol and IC.

13.2 Treatment Discontinuation

Upon treatment discontinuation, all end-of-treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study levels. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary. In addition, patients will be withdrawn from treatment in the case of:

1 RANO criteria defined disease progression. In cases where RANO criteria cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.

2 A need for cranial surgery to resect tumor or reduce mass effect, further radiation therapy or stereotactic radiosurgery, or for other anticancer therapy not specified in the protocol.

3 Lost to follow-up or noncompliant.

4 Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

5 Death.

6 Participant's voluntary withdrawal

- A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.

7 Investigator judgment.

14 EFFICACY EVALUATIONS

14.1 Overview

All imaging studies, except for the post-op MRI scan (≤ 72 hours after craniotomy), must be performed at qualified investigative sites or at a sponsor-approved facility using the protocol-defined imaging parameters listed in the Imaging Manual. Determination of initial eligibility, continuing eligibility at baseline and tumor progression will be performed by the local PI in collaboration with a neuroradiologist at the participating institution as required. Blinded central radiology review of images at specific stages will be performed in parallel for correlative study of progression-free survival. There will be no collaboration between Central Imaging and participating centers, other than for matters related to data transfer.

14.2 Evaluation of Tumor Progression (MRI Scans for Disease Assessment)

All MRI scans performed for continuing disease assessment in connection with this study must be performed at a qualified enrolling site and be provided to the Central Imaging for correlative analysis. Scans that are performed at non-enrolling sites or that are performed using parameters not specified in this protocol should not be used for disease assessment or determination of tumor progression in connection with this study, except following consultation with the Medical Monitor. Any interim MRI scans obtained for standard of care after randomization will be collected. MRI scans for disease assessment should be obtained more than 2 days, but not more than 10 days, before each date of vaccine administration in the VM stage, which coincides with the first of five days of every other 28-day TMZ cycle, whenever possible. Tumor progression should be determined according to RANO criteria **(Appendix B).**

14.3 Decisions Regarding Tumor Progression

The date of tumor progression will be determined by the local PI in collaboration with the local neuroradiologist at the participating center. The local PI will have final authority to determine whether tumor progression has occurred and whether it is in the best interest of the patient to continue on protocol. Every effort should be made to follow RANO criteria in making this determination **(Appendix B).** Blinded Central Imaging review of disease assessment MRI scans will be used to obtain correlative analysis of progression-free survival (PFS) as primary and secondary endpoints. There will be no collaboration between Central Imaging and participating centers with regard to determination of tumor progression.

14.4 Progression-free Survival (PFS) Analysis

The duration of progression-free survival (PFS) is defined as the time from the date of randomization until the date of clinical evaluation that confirms progressive disease. Response Assessment in Neuro-Oncology (RANO) criteria **(Appendix B)** will be used to determine tumor progression and responses to treatment (21). RANO considers MRI results, neurologic status, and steroid dosing. According to these criteria, progression of disease will be assumed if any of the following criteria are met:

- ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids
- Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects)
- Any new lesion or development of multicentric, leptomeningeal or spinal disease
- Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, adverse effects of medication, complications of therapy, cerebrovascular events, infection) or changes in corticosteroid dose
- Failure to return for evaluation as a result of death or deteriorating condition; or clear progression of non-measurable disease

14.5 Pseudo-progression (PsP)

Since this is a study of patients with newly diagnosed glioblastoma treated with radiation therapy and active immunotherapy, when new enhancement is seen on an MRI scan, every effort must be made to determine the presence of pseudo-progression and immune-based inflammatory changes and to distinguish these changes from true tumor progression. Approximately 25% of patients with glioblastoma who receive chemoradiation for newly diagnosed glioblastoma exhibit a transient increase in tumor enhancement that eventually subsides without change in therapy (pseudo-progression). This protocol allows for investigators to confirm progression before removal of patients from study treatment, thus ensuring radiographic follow-up to a valid disease progression time point. Dynamic susceptibility contrast (DSC) imaging will be used to assist in the determination of pseudo-progression. If there is uncertainty about whether new enhancement may

represent pseudo-progression, patients may continue under treatment on protocol and remain under close observation and evaluation with MRI scans at four-week intervals as long as the patient is clinically stable and without increased steroid dose. If subsequent evaluations indicate that the patient has true tumor progression, the date of progression must be recorded as the time point at which this question was first raised (i.e., the date of the MRI scan that first revealed the RANO-defined progression).

14.6 Re-biopsy to Assess Tumor Progression Versus Pseudo-progression

If a patient who has completed the 4-dose vaccine priming phase of treatment undergoes either biopsy or re-resection by craniotomy for new contrast-enhancing tissue, and no tumor whatsoever is determined by the neuropathologist to be present on histologic exam, the patient may continue on protocol with approval of the Medical Monitor. If any amount of tumor is found to be present at re-biopsy/re-resection, the patient should be declared to have tumor progression as of the date of the MRI scan that first showed the RANO-defined changes. Patients with new enhancement during the priming phase that is judged to be true tumor progression are not eligible to continue treatment on protocol. In all such instances, DSC imaging techniques should be employed to assist in that determination.

14.7 Blinded Central Imaging Review

Blinded central radiology review will be employed at specific stages of assessment, including for determination of: 1) initial eligibility (post-op MRI scan), 2) continuing eligibility (baseline MRI scan following chemoradiation), and 3) tumor progression during regular disease assessments just prior to every other 28-day chemotherapy (i.e. every vaccine) cycle. Defined imaging parameters will be used to characterize tumor status at baseline and during follow-up. RANO criteria will be used to assess tumor progression with and without perfusion-weighted imaging techniques. **All decisions regarding initial eligibility, continuing eligibility at baseline, and tumor progression, will be made by the local PI in consultation with the local neuroradiologist.** Central Imaging will be blinded to treatment arm and will not provide consultative advice or guidance to the PIs at enrollment sites. Data regarding progression-free survival, as determined by local assessment, will be used by the individual PIs to determine continuation under treatment on protocol. Data regarding progression-free survival, as determined by Central Imaging, will be collected and evaluated in a correlative fashion as a co-primary endpoint.

15 SAFETY MANAGEMENT

15.1 Data Safety Monitoring Committee

The Independent Data Safety Monitoring Committee (IDSMC) will assess the progress of the study, safety data and critical efficacy endpoints at a minimum of six (6) month intervals. The DSMC will review the study and will make recommendations that include but are not be limited to; (a) continuation of the study, (b) modifications to the design, and (c) termination of the study.

15.2 Adverse Events Definitions

The Investigator will monitor the occurrence of AEs during the course of the study and for 30 days after the administration of the last dose of study drug.

The following definitions of terms are guided by the International Conference on Harmonisation and the United States Code of Federal Regulations and are included here verbatim.

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's brochure or is not listed at the specificity or severity that has been observed; or, if the Investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

15.3 Classification of Adverse Events by Severity

Toxicities will be assessed according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), v5.0 (**Appendix D**). When the NCI-CTCAE grade is not available, the Investigator will use the following toxicity grading: mild, moderate, severe, life threatening, or fatal.

Grade 1: Grade 1 found on the CTCAE table or if not found in the toxicity tables, an AE that is transient or mild discomfort, not interfering with the patient's daily activity performance or functioning; medical intervention/therapy may be required.

Grade 2: Grade 2 found on the CTCAE table or if not found in the toxicity tables, an AE of sufficient severity as to possibly make the patient moderately uncomfortable; possibly influencing the patient's daily activity performance or functioning; generally not impairing the patient's ability to continue in the study; and/or possibly needing therapeutic intervention.

Grade 3: Grade 3 found in the CTCAE table or if not found in the toxicity tables, an AE event generally causing severe discomfort, significantly influencing the patient's daily activity performance or functioning, generally requiring alteration or cessation of study drug administration, and/or generally requiring therapeutic intervention with hospitalization possible.

Grade 4: Grade 4 found in the CTCAE table or if not found in the toxicity tables, an AE that is considered to be life threatening, resulting in significant disability or incapacity, and/or representing the worst possible occurrence of that event with hospitalization probable.

15.4 Causality

Under this protocol, four (4) distinct active drugs will be administered, including: TMZ, SurVaxM, Montanide and sargramostim. The relationship of each AE to each study drug administration will be assessed by the Investigator; after careful consideration, according to the following guidelines:

NOT RELATED: This category is applicable to those AEs that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and/or the clinically plausible temporal sequence is inconsistent with the onset of the event and the administration of the study drug and do not meet the criteria for drug relationship listed under UNLIKELY, POSSIBLY, PROBABLY, or DEFINITELY RELATED.

UNLIKELY RELATED: This category is applicable to those AEs that could easily be explained by the patient's clinical status or other factors and/or there is a poor temporal relationship with the administration of the study drug.

POSSIBLY RELATED: This category applies to those AEs that, are judged to be perhaps related to the study drug administration. An AE may be considered POSSIBLY RELATED when it meets at least *one* of the following criteria:

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It follows a known or expected response pattern to the study drug.

PROBABLY RELATED: This category applies to those AEs that are assessed with a high degree of certainty by the Investigator to be related to the study drug administration. An AE may be considered PROBABLY RELATED if it meets at least *two* of the following criteria:

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
3. It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., depression, fixed drug eruptions, tardive dyskinesia, etc.).
4. It follows a known or expected response pattern to the study drug.

DEFINITELY RELATED: This category applies to those AEs that are incontrovertibly related to study drug administration. An AE may be assigned to this category if it meets at least the first *three* of the following criteria:

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., depression, fixed drug eruptions, tardive dyskinesia, etc.).
4. It follows a known or expected response pattern to the study drug.
5. It reappears or worsens when the study drug is re-administered.

15.5 Reporting of Adverse Events

15.5.1 Adverse Events

The safety of all patients enrolled in this study will be recorded from the time of the first dose of study drug is administered, throughout the course of the study, and for 30 days after the last dose of study drug. This includes both serious and nonserious AEs.

All AEs will be recorded in the appropriate section of the eCRF. Patients withdrawn from the study because of AEs will be followed by the investigator until the outcome is determined. When appropriate, additional written reports and documentation will be provided.

Any unexpected AE ≥NCI-CTCAE Grade 3 event that occurs during this study and up to 30 days after discontinuation of study drug, regardless of relationship, should be reported to the Medical Monitor.

The PI or a qualified designated staff physician will conduct clinical assessments on all patients at each scheduled clinic visit. In addition, patients will be queried about any adverse symptoms they have experienced since the previous study visit. In order to avoid bias in eliciting events, suggestive questioning of the patients shall not occur.

AEs will be reported and described in terms of intensity, seriousness, and causality, based on the Investigator's judgment using protocol defined definitions. Necessary counter measures will also be reported on the appropriate eCRF used to collect concomitant medications.

15.5.2 Reporting Laboratory Abnormalities

For this study all Grade 3 and 4 nonhematologic laboratory toxicities and hematologic laboratory toxicities will be listed as AEs. To the extent possible, all laboratory abnormalities observed during the course of the study will be included under a reported AE describing a clinical syndrome (e.g., elevated blood urea nitrogen and creatinine in the setting of an AE of "renal failure" or elevated ALT/AST in the setting of an AE of "hepatitis"). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

In the absence of a reported AE identifying a clinical syndrome that encompasses the observed laboratory abnormality that "isolated" laboratory abnormality itself should be reported as an AE. The criteria for "clinically significant" laboratory abnormalities include a laboratory abnormality that leads to a DLT (i.e., judged to be associated with study drug administration and resulting in study drug dose reduction, suspension or discontinuation) or a laboratory abnormality that results in any treatment-emergent therapeutic intervention (i.e., concomitant medication or therapy), or any other laboratory abnormality judged by the Investigator to be of other particular clinical relevance.

Patients experiencing AEs or laboratory abnormalities will be assessed and appropriate evaluations performed until all parameters have returned to baseline levels or are consistent with the patient's then-current physical condition.

15.5.3 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

15.5.4 Pre-existing Medical Conditions (Baseline Conditions)

A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

15.5.5 Severity Assessment of Injection Site Reaction

Measurement of any local skin reaction that may occur once the patient leaves the clinic should be reported by the patient or caregiver. At the time of injection, the patient/caregiver will be instructed by the study staff to measure the area of local reaction at its perceived maximum (using the diameter of a U.S. quarter – approximately 1 inch – as a reference standard), between 24 to 48 hours of administration of dosing emulsion. Patients (or caregivers) will be asked to record the approximate dimensions of the reaction (if any) and the date it was measured. The study coordinator will contact the patient (or caregiver) within 3 to 5 days after the injection to obtain and record the patient's local reaction measurement.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Injection Site Reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Acneiform or Papulopustular Rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Maculo-papular rash	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL		
Pustular rash		Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative		
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL		
Induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death

BSA = Body Surface Area

ADL = Activities of daily living.

15.6 Serious Adverse Events

Instructions for reporting Serious Adverse Events are found in Section 15 and the Safety Management Plan. Any SAE that occurs during this study from the time of the first dose through up to 30 days after discontinuation of study drug must be reported according to the procedures in Section 15 and the Safety Management Plan within 24 hours of the PI's awareness of the event, whether or not this reaction is considered to be associated with the use of the study drug. In addition, the occurrence of any AE leading to permanent discontinuation of study drug must also be reported to the Sponsor within 24 hours of the PI's awareness of the event.

A written report of all SAEs and deaths that occur between the first administration of study drug and 30 days after administration of the last dose must be submitted to the IRB/ethics committee (EC) and the Sponsor. SAE's which are both serious and unexpected, based on the described profile of the drug and its non-clinical safety evaluation, must be reported to the Sponsor within 24 hours for a determination of expedited reporting to FDA, as described in Section 15.5. In all SAE reports, the Investigator will advise whether or not the SAE is judged to be related to study drug administration. SAEs and deaths that occur more than 30 days after administration of the last dose and are not reasonably associated with study drug do not require reporting. All SAEs that are judged by the Investigator to be at least possibly related to study drug administration must be reported to the Sponsor or its designee regardless of how much time has elapsed since the last exposure to study drug. All nonserious AEs must be submitted to the IRB/EC in an annual report.

15.7 Reporting of Pregnancies

If a patient, including the female partners of a male study patient becomes pregnant during the course of the study, the Investigator or site personnel must notify according to the procedures in

Section 15 and the Safety Management Plan within 5 working days after the Investigator or site personnel become aware of the pregnancy. If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (within 24 hours) must be met. The patient will be immediately discontinued as outlined is Section 13.2. The patient will be followed through the term of the pregnancy.

15.8 Disease Progression

If the progression of the underlying disease (i.e., the condition being treated with study drug) might be reasonably anticipated given the nature and severity of the underlying disease, then progression of the underlying disease per se will not constitute an AE. However, if the progression of the underlying disease meets the criterion for "serious" categorization of AEs (e.g., the underlying disease results in death or hospitalization), then the progression of underlying disease should be reported as an SAE (see Section 15.6).

15.9 Overdoses

Overdoses should be reported as a protocol violation. If an overdose results in an AE, the eCRF AE page should be completed and attach source documents. If the overdose results in an SAE, then SAE reporting should be followed using the specific eCRF pages with overdose information entered in the narrative section. All available clinical information relevant to overdose, including signs and symptoms, laboratory findings, and therapeutic measures or treatments administered, should be summarized and discussed.

15.10 Adverse Events Qualifying for Reporting to Regulatory Authorities

Expedited adverse events are to be reported to the Sponsor, CRO and Medical Monitor within 24 hours according to the procedures on in Section 15 and the Safety Management Plan. An adverse event deemed a suspected adverse reaction that is both serious and unexpected will be reported to the regulatory authorities by Sponsor in accordance with 21 CFR §312.32. Serious, unexpected, suspected adverse reactions (SUSARs) will be reported to the regulatory authorities within 15 calendar days of initial notification to Sponsor or its designee. If the suspected adverse reaction is serious and unexpected, and is fatal or life threatening, the event will also be reported by phone or fax to the regulatory authorities within 7 calendar days.

16 DRUG INFORMATION

16.1 SurVaxM (SVN53-67/M57-KLH)

The synthetic peptide in SurVaxM (SVN53-67/M57) includes amino acids 53 through 67 of the human and mouse survivin protein sequences with a substitution of methionine (M) for cysteine (C) at position 57 which leads to enhanced MHC class I (HLA-A*02) binding. The peptide is conjugated to Keyhole Limpet Hemocyanin (KLH). SVN53-67/M57-KLH contains a peptide mimic that is immunogenic in humans and in C57BL/6 mice. This clinical investigational study is based on extensive experimental observation concerning the ability of SurVaxM to elicit potent and specific immune responses against survivin-expressing tumor cells.

SurVaxM (SVN53-67/M57-KLH) is a peptide-KLH conjugate and is intended to be used as a cancer vaccine. It is a biological drug by class. It is chemically conjugated to Keyhole Limpet Hemocyanin (KLH), which serves as a carrier protein and immune adjuvant.

SurVaxM is supplied for this trial by MimiVax, LLC (Buffalo, NY). It is administered in emulsion with Montanide ISA 51, (Cross-Referenced Drug Master File 10870, Seppic, Inc. France). The emulsion is co-administered with a separate local injection of sargramostim (recombinant human GM-CSF; Leukine®) to facilitate attraction and maturation of local antigen presenting cells (APC) which ingest, process and present survivin peptide epitopes to the immune system.

SurVaxM is shipped as a sterile lyophilized powder (1 mg/vial) in 2 mL clear borosilicate glass vials with crimped rubber stoppers. Labeled boxes of SurVaxM (SVN53-67/M57-KLH) are shipped to sites. SVN53-67/M57-KLH (SurVaxM) must be stored at -20°C as outlined in Pharmacy Manual. SurVaxM in its solid lyophilized state has been shown to be stable for over 5 years at -20°C. SurVaxM should be handled and disposed of according to the instructions in the Pharmacy Manual.

SurVaxM should be reconstituted according to the instructions in the Pharmacy Manual. The reconstituted solution must either be used for vaccine preparation or discarded.

16.1.1 Preparation of SurVaxM Emulsion with Montanide® ISA 51

For patients in Arm A, SurVaxM will be mixed by rapid sequence with Montanide® ISA-51 to create an emulsion using the procedures outlined in the Pharmacy Manual.

16.1.2 Preparation of Saline Emulsion (i.e., Placebo) with Montanide® ISA 51

For patients in Arm B, saline will be mixed by rapid sequence with Montanide® ISA-51 to create an emulsion using the established procedures outlined in the Pharmacy Manual.

16.2 Storage and Preparation of Sargramostim

Sargramostim is an approved drug (NDC Product Code 50419). It is obtained as a lyophilized powder in 250 mcg vials and is stored refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect it from light. Do not freeze or shake. For use in patients in Arm A, sargramostim will be reconstituted in sterile water or bacteriostatic water (250 mcg/1 mL). The preparation will be administered locally as a second separate injection (100 mcg sargramostim or 0.4 mL) within 1-3 cm of the site of the SurVaxM-Montanide emulsion injection. Do not use sargramostim beyond the expiration date printed on the vial. Sargramostim should be used within 6 hours following reconstitution. Do not re-enter or reuse the vial. Discard any unused portion. Patients in Arm B will receive 0.4 mL saline instead of sargramostim administered within 1-3 cm of the site of the saline-Montanide emulsion injection.

16.3 Adjuvant temozolomide (TMZ)

All patients enrolled in this trial will receive adjuvant temozolomide as part of standard of care treatment for newly diagnosed glioblastoma. Temozolomide is approved by USFDA as a standard treatment for newly diagnosed glioblastoma.

17 DATA RECORDING AND eCRF PROCESSING,

17.1 Data Recording and eCRF Processing

Data for this study will be recorded in the patient's source documents and into an eCRF system that must be kept current to reflect patient status during each part of the study. Patients are not to be identified by name on the eCRF. The eCRFs are not to be used as source documents.

Appropriately coded identification (site number, patient identification number, and patient initials) should be used. All data should be recorded completely and promptly in the eCRFs as soon after the visit as possible, but no later than 5 days. All queries are to be answered within 3 days of query date.

The Electronic Data Capture (EDC) system has been validated and is compliant with Food and Drug Administration (FDA), ICH, and European Union (EU) regulations and guidelines and with Department of Health and Human Services 21 CFR Part 11 rules for electronic records and electronic signatures. No data will be requested other than what is routinely entered in the eCRFs.

An audit may be performed at any time during or after completion of the clinical study by Sponsor personnel, their designee, and any relevant regulatory or ethics committees. All study-related documentation must be made available to the designated auditor.

18 STATISTICAL PLAN

18.1 Study Objectives

18.1.1 Primary Objective

- To compare overall survival in patients with newly diagnosed glioblastoma between treatment arms A and B.

18.1.2 Secondary Objectives

- To tabulate the number and type of grade 3 and grade 4 toxicities, according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAEs) Version 5.
- To compare progression-free survival in patients with newly diagnosed glioblastoma between treatment Arms A and B.
- To compare treatment-associated overall survival at pre-specified time points (OS-15, OS-18 and OS-24) between treatment Arms A and B.
- To compare treatment-associated progression-free survival at pre-specified time points (PFS-3, PFS-6 and PFS-12) between treatment arms A and B.

18.1.3 Exploratory and Scientific Objectives

- To evaluate the predictive value of perfusion-weighted imaging in assessing pseudo-progression and post-vaccination enhancement in patients receiving SurVaxM
- To evaluate the objective image-based tumor response rate (applicable only for patients with evaluable disease at study entry as defined by RANO criteria).
- To evaluate molecular predictors of response to SurVaxM, including MGMT methylation status, anti-survivin immunoglobin titers, survivin-specific CD8+ responses, tumor survivin expression levels and other molecular tumor tissue markers.

18.2 Study Endpoint Definitions

18.2.1 Primary Endpoint:

- OS is defined as the time from date of randomization to death due to any cause.

18.2.2 Secondary Endpoint:

- PFS is defined as the time from the date of randomization to the date of first observed disease progression or death due to any cause.

18.3 Hypotheses

H_{01}: The hazard ratio of subjects randomized to SurVaxM compared to subjects randomized to control for overall survival = 1.00

H_{11}: The hazard ratio of subjects randomized to SurVaxM compared to subjects randomized to control for overall survival < 1.00 (favoring SurVaxM)

Hypothesis testing will be completed at a two-sided Type I error of 0.05. If H_{01} is rejected in favor of H_{11} the study will be considered a success.

18.4 Statistical Plan

This trial is designed as a parallel-groups, 3:2 randomized placebo-controlled trial of SurVaxM as add-on therapy to standard of care temozolomide for newly diagnosed glioblastoma. The primary endpoint is overall survival (OS) from time of randomization. The sample size will be n_1=159 in the SurVaxM arm and n_2=106 in the control arm for a total sample size of n_1+n_2=265. If OS is demonstrated to be statistically superior for SurVaxM over control, the study will be considered a success.

All subjects meeting the eligibility criteria who sign a consent form and have been randomized to receive either SurVaxM or control will be considered evaluable for efficacy analysis (ITT). Safety analysis will be performed on all patients who have signed a consent form and received at least one dose of the study drug. Subjects will be followed for survival status after completion or discontinuation of the study drug and for progression or discontinuation of the study drug for other reasons.

All data collected will be summarized and presented. Continuous variables will be described as the mean, median, standard deviation and range of the observations. Categorical data will be described with contingency tables including frequency and percentage. Individual patient listings will be generated and presented. Differences between treatment groups will be calculated as SurVaxM – control and change from baseline will be calculated as follow-up visit – baseline. Baseline values will be defined as the last non-missing measure prior to initiation of investigational product. All efficacy analyses will use a 2-sided alpha = 0.05 test unless otherwise stated and corresponding 2-sided 95% confidence intervals (CIs) will be presented as applicable.

Statistical descriptions and analyses will be carried out using SAS statistical analysis software version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

18.4.1 Analysis Populations

- Intention to Treat (ITT) – the ITT population will include all subjects randomized into the study. Subjects will be analyzed according to the treatment group to which they were randomized.

- Per Protocol (PP) – the PP population will include all ITT subjects who do not have significant protocol deviations likely affecting the primary endpoint analysis. Protocol deviations will be assessed prior to unblinding for scheduled analyses.
- Safety – the Safety population will include all subjects who receive any amount of investigational product. Subjects in the safety population will be analyzed as treated.

18.4.2 Sample Size Justification

18.4.2.1 Overall Survival

Assuming a 1-year survival rate of 75% in the SurVaxM group (Arm A; comparable to a median overall survival (mOS) of 29 months assuming an exponential distribution) and 60% in the control group (Arm B; comparable to an mOS of 16 months assuming an exponential distribution), approximately 159 subjects will be randomized to SurVaxM and 106 subjects randomized to control.

The analysis of this endpoint is event-driven and will complete when 142 deaths (combined across the 2 treatment groups) occur, assuming that the study had not been stopped earlier for efficacy or safety considerations, and assuming the study is not extended through the promising zone methodology. With 142 deaths, the study has approximately 90% power to detect a 44% reduction in the risk of death (HR = 0.56) in the SurVaxM group (versus control) with an overall 2-sided Type I error of 5%.

Approximately 265 subjects will be randomized 3:2 between SurVaxM and control over an approximate 18-month period. Assuming uniform accrual over the 18-month period, exponential survival on both SurVaxM (1-year survival of 75%) and control (1-year survival of 60%), the targeted number of deaths is expected at month 35 (17 months after the last subject starts treatment). Deviations from this assumption are controlled by an event-driven approach: the final analysis will occur once the targeted number of deaths is accrued.

An interim futility and efficacy analysis for OS is planned once 50% of the deaths (71 deaths) are accrued in the study. Information regarding the stopping rules for the interim analysis is provided in **Section 18.4.3**.

18.4.3 Interim Analysis

There will be a single planned group sequential interim analysis conducted for efficacy when 50% of the planned number of deaths (71 deaths) have occurred. The interim analysis will be event driven and will evaluate efficacy with respect to the OS endpoint. The Pocock alpha spending function will be used to allocate the overall 2-sided Type I error of 0.045 to the interim and final analyses. In the event that the interim analysis occurs earlier or later than planned, this spending rule will enable the adjustment of the alpha spending to the changes in the interim analysis timing.

The **Table 3** below provides the projected stopping rules if the interim analysis is conducted at the projected number of deaths.

Table 3: Stopping Rules From Interim Analysis

	Interim Analysis		**Final Analysis**	
Projected Timing	20 Months		35 Months	
Projected Enrollment	265		265	
Combined # of Deaths	71 (50%)		142	
Decision	**Continue**	**Stop Efficacy**	**Do Not Reject H_0**	**Reject H_0**
Efficacy Boundary	<2.1570	≥2.1570	<2.2009	≥2.2009
1-sided p-value	>0.01550	≤0.01550	>0.01387	≤0.01387

At the interim analysis with 50% of the information (deaths), if the one-sided p-value does not meet the requirement to stop the study early for efficacy (≤0.01550) the conditional power (CP) of the study will be calculated (using the final one-sided alpha = 0.01387) toward implementing the promising zone methodology from Mehta and Pocock (2011) with the following zones defined (assuming a maximum increase in events of 50%; note the zones will be updated based on the actual number of events at the interim):

- Unfavorable Zone – CP < 39.6%
- Promising Zone – 39.6% ≤ CP < 90%
- Favorable Zone – CP ≥ 90%

If the CP based on the interim analysis falls in the Promising Zone, the Sponsor has the option to increase the number of events and sample size to obtain a conditional power of 90% for the final analysis or to the maximum number of events allowed (213; a 50% increase over 142), whichever is smaller. If the CP falls in the Favorable Zone, the study will continue to the original protocol stated number of events and no adjustment is necessary. If the CP falls in the Unfavorable Zone, the sponsor may either stop the trial for futility or continue to the original protocol stated number of events.

If the decision is made, based on the Promising Zones, to increase the sample size to the maximum number of events allowed and the final analysis is completed on less than the maximum number of events, the final one-sided alpha will be adjusted using the critical value $b(z_1, \tilde{n}_2^*)$ as calculated in Lemma 1, Equations (10 & 11) in Section 3.2 of Mehta and Pocock 2011 with z_1 as the derived critical value from the planned Promising Zone boundary.

18.4.4 Randomization

Subjects will be randomized to SurVaxM versus control stratified on KPS (70-80/90-100), MGMT status (methylated/unmethylated), and IDH-1 status (mutant/wild type). Strata will employ random block sizes of 5. Patients will be randomized to the treatment arm (Arm A) and the placebo arm (Arm B) in a 3:2 ratio. The randomization lists to be used in this study will be generated by an independent biostatistician. Patients will be included in the data analysis according to their randomized treatment assignment irrespective of the treatment actually received (intent to treat). Patient randomization will be performed by the designated contract research organization which will direct the external research pharmacies at the various participating centers/sites regarding treatment arm designation of enrolled subjects.

18.4.5 Study Duration and Completion

All patients will be followed until death to determine overall survival. Patients who complete the study follow-up through study closure or die will be considered to have "completed" the study. The final analysis will occur after 142 deaths (assuming that the study had not been stopped earlier for efficacy or safety considerations and assuming the study is not extended through the promising zone methodology). It is anticipated that the enrollment period will be 18 months and follow-up will continue for 18 months after enrollment of the last patient placed on-study. Therefore, the study duration is expected to be 36 months.

18.4.6 Primary Efficacy Analyses

18.4.6.1 Overall Survival

The primary efficacy variable OS is defined as number of days from randomization to death due to any cause. The primary analysis for OS will be based on the ITT population, according to the treatment group to which the subject was randomized. A log-rank test stratified by KPS (70-80/90-100), MGMT status (methylated/unmethylated), and IDH-1 status (mutant/wild type) will be used as the primary analysis. Median survival will be estimated using the Kaplan-Meier method. Confidence intervals for median survival time will be calculated using the method of Brookmeyer and Crowley. The HR and 95% CI will be determined using a stratified Cox regression model, using the same strata as covariates, with Efron's likelihood approximation to account for ties in event times. Sensitivity analyses for the primary endpoint will be conducted using the Max-combo test as well as repeating analyses using the PP population.

18.4.7 Secondary Efficacy Analyses

The secondary efficacy variable PFS is defined as number of days from randomization to the date of first observed disease progression or death due to any cause. The primary analysis for the secondary efficacy variable PFS will be based on the ITT population, according to the treatment group to which the subject was randomized. Progression free survival data will be analyzed similarly to overall survival. Event and censoring dates will be applied as detailed in the formal statistical analysis plan based on FDA guidance.

Secondary endpoints of OS and PFS rates at stated time points will be estimated along with 2-sided 95% CIs will be estimated using the Kaplan-Meier method.

Additional secondary analysis of, OS and PFS, will be repeated by relevant demographic and baseline characteristic subgroups including KPS, MGMT status, and IDH-1 status.

18.4.8 Prior and Concomitant Medication

All relevant prior medication and all concomitant medications will be summarized.

18.4.9 Safety and Toxicity Analyses

Adverse events monitoring and clinical findings including physical examinations, vital signs, laboratory test results, concomitant medications, and withdrawals/terminations will be used to assess safety.

18.4.10Adverse Events and Serious Adverse Events

AEs will be categorized by SOC and Preferred Terms as per CTCAE version 5.0. The incidence of AEs as well as the severity and relationship to individual study drugs will be presented by treatment arm. The incidence of AEs leading to withdrawal from study of the investigational product and serious AEs (SAEs) will be summarized by frequency and percentages.

As per NCI CTCAE Version 5.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient and will be used for reporting. Frequency tables will be reviewed to determine toxicity patterns. In addition, all adverse event data graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing will be reviewed.

Serious adverse events will be similarly summarized. Clinical findings will include evaluation of physical examinations, vital signs and laboratory test results, concomitant medications, and withdrawals/terminations. These findings will be summarized by treatment group.

18.4.11 Procedure for Accounting for Missing, Unused and Spurious Data

Limited missing survival data are anticipated; every attempt will be made to follow subjects to obtain their survival data. Formal handling of missing OS and PFS data will be detailed in the statistical analysis plan, including sensitivity analyses to determine the robustness of results to the imputation of missing data. Missing data will be indicated in the listings but excluded from all descriptive analyses. All data will be listed, including otherwise unused data.

18.4.12 Demographics and Baseline Characteristics: Descriptive Analyses

Subject demographics comprising age, gender, race, and ethnicity as well as baseline characteristics will be presented using discrete or continuous summary statistics as appropriate.

18.4.13 Safety Analysis

Safety and tolerability will be assessed by incidence, severity, and changes from baseline of all relevant parameters including adverse events (AEs), laboratory values and vital signs.

Vital sign results (systolic and diastolic blood pressure, pulse, respiration, and temperature) will be summarized descriptively for each scheduled and unscheduled protocol time point. Changes will be calculated relative to the assessments at baseline.

The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled and unscheduled protocol assessment time point. Changes will be calculated relative to the values collected at baseline. Data listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in data listings and will include flags for high and low values.

The frequency of toxicities will be tabulated by grade. All participants who receive any study treatment will be considered evaluable for toxicity.

18.4.14 Adverse Event Analysis

AEs will be coded using the latest available version of the NCI CTCAE (v5.0). AEs will be summarized for each treatment arm by the number and percentage of patients who experienced the

event, according to system organ class and preferred term. Additional summaries will also be provided by severity grade and relationship to study drug, and for SAEs and events resulting in the permanent discontinuation of therapy. A patient reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term, and adverse events will be graded by worst severity grade. Unless specified otherwise, the denominator for these calculations will be based on the number of patients in each treatment arm who receive at least one dose of study drug, irrespective of the total number of doses administered. All participants who receive any study treatment will be considered evaluable for toxicity.

18.4.15 Withdrawal and Replacement of Patients

Every reasonable effort should be made within the bounds of patient safety to have each subject complete the study. Patients who begin study treatment should continue to be followed for OS and PFS regardless of whether or not the subject discontinues treatment. Reasons for discontinuation of study treatment may include:

- Receipt of alternate anti-cancer therapy.
- Development of unacceptable toxicity.
- Withdrawal of consent for study treatment by the subject or the subject's legal representative
- If, in the investigator's medical judgment, further participation would be injurious to the subject's health or well-being.
- Non-compliance of the subject.
- Pregnancy.
- Patient lost to follow-up.

A subject should be considered lost to follow-up only after significant effort has been made to contact the individual to assess his/her health status after failure of the subject to attend scheduled visits. If the investigative site is still unable to contact the subject after three documented phone calls, a certified letter should be sent to his/her home for immediate response. If there is still no response, the subject should be considered to be lost to follow-up. A record of the subject being lost to follow-up should be noted in the source documents along with the phone contacts and the returned certified mail (if sent back).

An explanation will be recorded for each subject that is taken off study treatment or upon discontinuation of study follow-up. Patients who discontinue treatment early should be seen for an End of Treatment Visit. When possible, patients who withdraw from post- treatment follow-up should be seen for a final Follow-up Visit.

Since this study utilizes an intent to treat analysis, there will be no replacement of randomized patients.

18.4.16 Criteria for Early Study Termination

Early termination of this study may occur because of a regulatory authority decision, patient safety, or at the discretion of either the Sponsor or MimiVax, LLC. In addition, MimiVax retains the right to discontinue development of SurVaxM at any time. If a study is prematurely terminated or

discontinued, the Sponsor will notify the investigator. Following such notification, the investigator must notify all participating patients and the hospital pharmacy as quickly as is reasonably possible. All study materials must be collected, and all case report forms must be completed to the extent possible.

18.4.17 Correlative Data Analysis

The following parameters will be analyzed to determine correlations with the primary and secondary efficacy endpoints, including completing subgroup analyses of the primary and secondary endpoints based on the baseline and change from baseline values. See Laboratory Manual for additional details on obtaining samples, sample processing and shipping.

18.4.17.1 Immunological Assessments

Immunologic responses to vaccine will be assessed in all patients. Survivin-specific CD8+ (cellular immune) and anti-survivin antibody (humoral) responses will be measured by the Immunotherapy Core Facility and the Neuro-oncology Laboratory at Roswell Park. PBMC and serum will be collected according to the schedule in Schedule of Procedures and Observations **Appendix C**. Samples will be processed and shipped according to the instructions in the Laboratory Manual. Cellular immunologic responses to SVN53-67/M57-KLH (SurVaxM) will be measured using multimers by flow cytometry. Antibodies to survivin peptides and KLH will be measured on serum samples by ELISA.

Immunological analyses will be conducted on blood samples obtained prior to vaccination (at baseline) and at specified study follow-up visits as outlined in the Schedule of Procedures and Observations **Appendix C**). Samples should be drawn and processed as specified in the Laboratory Manual. Peripheral blood mononuclear cells (PBMC) will be processed, stored, and shipped according to the procedures outlined in the Laboratory Manual.

18.4.17.2 Survivin Expression in Tumors

Over 98% of the patients screened for inclusion in a phase II study of SurVaxM had survivin protein expression in their tumors that was detectable by immunohistochemistry. Therefore, survivin expression will not be tested to determine eligibility. However, all enrolling sites will prepare and submit tissue blocks as outlined in the Laboratory Manual for survivin measurement for correlative studies.

18.4.17.3 MGMT

The O(6)-methylguanine-DNA methyltransferase (MGMT) gene is expressed in glioblastoma cells. Methylation of the MGMT gene promoter is associated with better response to temozolomide chemotherapy and measurement of MGMT methylation status is part of the standard assessment of patients with newly diagnosed glioblastoma. All patients must have MGMT methylation status determined locally prior to randomization as part of standard-of-care management.

18.4.17.4 Isocitrate Dehydrogenase (IDH)

Isocitrate dehydrogenase (IDH) mutations are associated with longer survival of patients with glioblastoma. All patients will have slides submitted for IDH-1 testing by immunohistochemistry locally. Results of IDH-1 testing will not be used to determine treatment. In addition, slides will be submitted on each patient for sequencing of IDH-1 and IDH-2 to identify mutations according

to the procedures as outlined in the Laboratory Manual. All patients must have IDH status determined locally prior to randomization as part of standard-of-care management.

18.4.17.5 Other Scientific Correlates

Tumor tissue from each patient will be submitted according to the procedures outlined in the Laboratory Manual for genomic profiling by Tempus and other partners. Associations between specific molecular profiles and both PFS and OS will be explored to determine if any tumor correlates predict treatment response or benefit from survivin vaccination compared to placebo. Results of molecular testing will not be used to determine treatment.

19 ADMINISTRATIVE ASPECTS

19.1 Institutional Review Board/Ethics Committee

This protocol and the proposed informed consent form must be reviewed and approved by the appropriate IRB/Ethics Committee (EC), prior to the start of the study. The proposed informed consent form must also be agreed to by the Sponsor or its designee. A copy of the IRB/EC approval letter of the protocol, any amendments, and the informed consent form must be supplied to the Sponsor or their designee prior to starting the study. During the course of the study, the Investigator shall make timely and accurate reports to the IRB/EC on the progress of the trial, at intervals not exceeding one year, as well as satisfying any other local IRB/EC regulations regarding reporting. Copies of all reports to and correspondence with and from the IRB/EC must be provided to the Sponsor or their designee.

Any significant changes or revisions in the study protocol or any changes that may alter patient risk must be approved by the Sponsor (and may require other review and/or approval) and must be approved in writing by the IRB/EC prior to implementation. A protocol change intended to eliminate an apparent immediate hazard may be implemented immediately provided that the Sponsor is immediately notified and an amendment is subsequently provided by the Sponsor and approved by the IRB/EC.

It is the Investigator's obligation to maintain an IRB/EC correspondence file, and to make this available for review by the Sponsor representatives or their designee as part of the study monitoring process.

19.2 Informed Consent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information (PHI) must be obtained from each patient (or the patient's legal representative) prior to performing any study-specific Screening Period evaluations. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) for valid authorizations. The proposed informed consent form must be in compliance with regulatory regulations and must have been reviewed and approved by the Sponsor and the Investigator’s IRB or IEC prior to initiation of the study. The proposed informed consent form should contain the 20 elements of informed consent described in ICH E6 4.8, including a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages, risks, alternate treatment options, and a statement of confidentiality of patient study records, a statement regarding voluntary compensation

and availability of treatment in the case of injury, an explanation of whom to contact about the research, the patient's rights, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits. These requirements are in accordance with the Code of Federal Regulations as detailed in the 21 CFR 50.25 and the Declaration of Helsinki. It should also indicate by signature that the patient, or where appropriate, legal guardian/representative, permits access to relevant medical records by the Sponsors staff, the Sponsors duly appointed representatives, and by representatives of the U.S. Food and Drug Administration (FDA) or other applicable regulatory agency. Additionally, Investigators in states with specific regulations regarding patient's rights have a responsibility to follow and document their fulfillment of those regulations.

The Investigator will be responsible for obtaining written informed consent from potential patients or the patient's legally authorized representative prior to any study specific screening and entry into the study. A copy of the signed document will be provided to the patient, and a copy will be maintained with the patient's records. The original will be retained by the Investigator. The source documents for each individual shall document that the informed consent was obtained prior to participation in the study.

19.3 Delegation of Investigator Responsibilities

The Investigator should ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and study related duties.

19.4 Study Documentation

19.4.1 Investigator Information

Investigator information is included in the Study Procedures Manual, which is updated regularly.

19.4.2 Laboratory Accreditation

Any laboratory facility to be used for analysis of routine clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation. Licensure/accreditations and reference values and/or normal ranges for the test results must be provided to the Sponsor or designee.

The Sponsor or designee must be notified immediately in writing of any changes occurring in reference values during the course of the study.

19.4.3 Study Files

Documentation concerning Investigator data and IRB data is required prior to shipment of study drug to the study site. Copies of these documents as well as supplemental information, such as the IB, will be kept on-site in an Investigator study file binder. This file also will contain drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB correspondence, changes to the protocol, information regarding monitoring activities, patient exclusion records, and biological sample records.

19.4.4 Source Documentation

The Investigator must make study data accessible to the Sponsor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors. The eCRF for each patient will be checked against source documents at the study site by the Study Monitor.

19.4.5 Retention of Study Documents (Investigator)

According to 21CFR312.62, all study documents including records of drug receipt and disposition, copies of eCRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of 2 years following notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as the Study Monitor, another Investigator, or the institution where the study was conducted. The sponsor should be notified in writing at least 30 days prior to the disposal of any study records related to this protocol.

19.5 Confidentiality

19.5.1 Data

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

19.5.2 Patient Privacy

The privacy of participating patients must be maintained. Patients will be identified by their initials and an assigned patient number on eCRFs, and other documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor that identify the patient (e.g., the signed informed consent document) and identifying information must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

19.6 Protocol Compliance

Substantive changes in the protocol include changes that affect the safety of patients or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of patients treated, or the patient selection criteria. Such changes must be prepared as a protocol amendment by the Study Monitor/project manager only upon joint approval of the Sponsor, Investigator, and the Study Monitor. A protocol amendment must receive IRB approval prior to implementation. In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the informed consent document, the revised informed consent document prepared by the Investigator must be reviewed by the Sponsor and the Study Monitor and approved by the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient and that are deemed crucial for the safety and well-being of that patient may be instituted for that patient only. The Investigator or other attending physician also will contact the Sponsor as soon as possible in the case of such a departure. These departures do not require

pre-approval by the IRB; however, the IRB and Sponsor must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the patient's eCRF the reasons for the protocol deviation and the ensuing events.

Protocol deviations that result from the COVID-19 pandemic will be aligned with and documented as outlined in the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards.

19.7 Monitoring Functions and Responsibility

Throughout the course of the study, the Sponsor's representatives, or monitors designated by the Sponsor, may make frequent contacts with the Investigator. This may include telephone and/or on-site visits at appropriate and necessary intervals.

The Investigator or appointed delegate will be available to the Sponsor's representative(s) during these on-site visits and will provide necessary study documents for inspection and will respond to all inquiries that may arise as part of this review. On completion of the study, the Sponsor's monitor(s) may arrange for a final review of the study files after which the file should be secured for the appropriate time period as specified in Section 19.4.5. The Investigator will also permit inspection of the study files by authorized representatives of the FDA or other applicable regulatory agency.

The progress of the study will be monitored by using the following methods:

- Periodic on-site visits
- Frequent telephone and written communications between the Investigator, Sponsor and the Study Monitors
- Review of eCRFs and clinical records

19.8 Drug Accountability

The study drug is to be prescribed only by the Principal Investigator or physician sub-investigators named on Form FDA 1572 and submitted to the IND. Under no circumstances will the Investigator(s) allow the study drug to be used other than as directed by this protocol.

19.9 Financial Disclosure

The Investigator and sub-investigators, as noted on the FDA Form 1572, shall provide the Sponsor with sufficient accurate financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements as required under 21 CFR 312.64.

The Investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

19.10 Patient Confidentiality

All reports and patient sample documents submitted with the Case Reporting Forms, or SAE reports, will be identified only by patient initials and study number (coded number) to maintain patient confidentiality. All records will be kept confidential to the extent permitted by law.

19.11 Disclosure of Data

All information obtained as a result of this study or during the conduct of this study will be regarded as confidential. Disclosures (i.e., any release of information to any third party not noted herein) of any, not previously known to be public, information and/or results of the investigation for publication or by capsules or poster presentation shall not be made earlier than 30 days after submission of the proposed material to the sponsor for inspection, unless the sponsor consents to earlier disclosure. The Investigator will take appropriate cognizance of the sponsor's suggestions before disclosure for publication or presentation consistent with protection of the sponsor's right to its confidential data.

19.12 Publication Agreement

The Sponsor recognizes the importance of and will fulfill its obligation for the timely disclosure of clinical research findings in appropriate forums. Any disclosure of results from the Sponsor's clinical trials will be submitted to the Sponsor for review to assure accuracy of information and to protect proprietary documents and materials. This review will not be unreasonably withheld and will be provided in writing within 30 days of receipt. Clinical trials conducted by more than one investigational site (i.e. multi-center studies) will be reported jointly with all patients represented in the analyses.

19.13 General Information

The Investigator should refer to the associated Investigator's Brochure, the Study Procedures Manual, information provided during the study initiation visit, information provided by the Study Monitor, and the appendices of this clinical study protocol for further information regarding this study drug or details of the procedures to be followed during the course of this study.

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21 TABLE OF APPENDICES

Appendix A Karnofsky Performance Status Scale

Status	Karnofsky
Normal, no complaints	100
Able to carry on normal activities. Minor signs or symptoms of disease	90
Normal activity with effort	80
Care for self. Unable to carry on normal activity or to do active work	70
Requires occasional assistance, but able to care for most of his needs	60
Requires considerable assistance and frequent medical care	50
Disabled. Requires special care and assistance	40
Severely disabled. Hospitalization indicated though death non-imminent	30
Very sick. Hospitalization necessary. Active supportive treatment necessary	20
Moribund	10
Dead	0

Appendix B Response Assessment in Neuro-Oncology (RANO)

RANO Criteria for Disease Assessment	
Response	**Criteria**
Complete Response	Requires all of the following: complete disappearance of all enhancing, measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically; note that patients with non-measurable disease only cannot have a complete response; the best response possible is stable disease
Partial Response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan and stable or improved clinically; note that patients with non-measurable disease only cannot have a partial response; the best response possible is stable disease
Stable Disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan; in the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose
Progressive Disease (≥ 12 weeks after radiation therapy completion)	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, adverse effects of medication, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of non-measurable disease

Appendix C Schedule of Procedures and Observations

Protocol Activity	Screen	Vaccine Priming Phase[1]				Adjuvant TMZ[2]		Maintenance Phase[3] and Disease Assessments	End of Treatment[4]	Survival Follow-up[5]
SurVaxM	V0	V1	V2	V3	V4	Day 1 of each 28-day cycle	Day 21 every cycle	Every 8 weeks (±1 week)		Every 8 weeks (±2 week)
Adjuvant TMZ				Start Adjuvant TMZ after V2, once AEs from prior chemoradiation revert to ≤ Grade 2; if possible, align TMZ Day 1 with vaccine dose to minimize patient burden.						
Obtain Informed Consent	X									
Obtain archival tumor tissue	X									
Obtain post-surgery MRI[9]	X									
Assess Baseline Symptoms		X								
Height and weight[18]	X	X	X	X	X	X		X		
Vital Signs[17]	X	X	X	X	X	X		X		
Medical and surgical history	X									
Concomitant medication	X	X	X	X	X	X		X	X	
Full Physical exam	X								X	
Abbreviated Physical Exam[26]		X	X	X	X	X		X		
Neurologic exam	X									
Focused neurologic exam[21]								X		
Karnofsky Status	X	X	X	X	X	X		X		
Hematology Labs[6]	X	X	X	X	X	X	X	X		
Chemistry Labs[7]	X	X	X	X	X	X		X		
Coagulation Parameters[24]	X							X[25]		
Urinalysis [22]	X									
Pregnancy Test[8]	X							X		

Protocol Activity	Screen	Vaccine Priming Phase[1]				Adjuvant TMZ[2]		Maintenance Phase[3] and Disease Assessments	End of Treatment[4]	Survival Follow-up[5]
SurVaxM	V0	V1	V2	V3	V4	Day 1 of each 28-day cycle	Day 21 every cycle	Every 8 weeks (±1 week)		Every 8 weeks (±2 week)
Adjuvant TMZ				Start Adjuvant TMZ after V2, once AEs from prior chemoradiation revert to ≤ Grade 2; if possible, align TMZ Day 1 with vaccine dose to minimize patient burden.						
HLA typing[13]	X									
Immune Profiling Labs[23]		X				X[27]			X	
Brain MRI (RANO)	X[10]							X[19]	X[20]	
Conduct Eligibility Assessment	X									
Vaccine (Arms A and B)		X	X	X	X			X		
Injection site assesment[14]		X	X	X	X			X		
Telephone follow up (+3 – 5 days)		X	X	X	X			X		
Adjuvant Temozolomide[16]						X[16]				
Treatment Assessment	X	X	X	X	X	X		X	X	X[11]
Adverse Events Assessment[12]		X	X	X	X	X		X	X	
Contact Information for survival follow-up									X	X
Patient Status Assessment										X[15]

Footnotes for Schedule of Procedures and Observations:

Note: *Unless otherwise noted, study assessments should be completed prior to dosing at each treatment visit.*

1. V1 begins within 7-28 days after completion of chemoradiation (once symptoms return to ≤ Grade 2) and then every two weeks (14 days ± 3 days) for a total of 4 doses (priming phase).
2. Adjuvant TMZ therapy (TMZ) will begin at a time point after V1, and approximately 28 days (± 14 days) (up to 8 weeks also acceptable). after completion of chemoradiation (once symptoms return to ≤ Grade 2). TMZ cycle is 28 days. Day 1 should be ± 3 days. Adjuvant TMZ will continue for 6-12 cycles at

the discretion of the investigator unless intolerance or tumor progression occurs. Temozolomide is to be taken on Day 1 through Day 5 of each 28-day cycle.

3. Maintenance Vaccine Phase: SurVaxM should be administered every 8 weeks (± 1 week) after the priming phase until intolerance, tumor progression or 24 months from first vaccination (V1).
4. The End of Treatment visit should be performed within 30 days of the last MRI scan that confirms tumor progression or prior to the initiation of alternate therapies (whichever occurs first). Follow-up and documentation of adverse events and concomitant medications should continue through day 30 (± 3 days), or until lost to follow-up or death.
5. Patients who discontinue study treatment should be followed on study for survival, with visits or phone contact every 8 weeks (± 2 weeks) until death or lost to follow-up.
6. Hematology: CBC with differential and platelets.
7. Chemistry: (CMP) defined as: chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmolality (calculated), anion gap. **NOTE:** Clinical blood chemistries may be performed on either serum or plasma unless otherwise indicated.
8. Pregnancy test is required for women of child-bearing potential only. A serum pregnancy test must be performed during screening. If the serum pregnancy test is not performed within 7 days of dosing on Priming Phase V1-Day 1, a urine pregnancy test must be performed on Priming Phase V1-Day 1 with results reviewed prior to dosing. Testing may be repeated throughout the study as indicated.
9. For initial eligibility determination, brain MRIs must have been obtained within 72 hours following craniotomy. Patients must have ≤1 cm^3 residual enhancing tissue on this scan to be eligible. Scans from other institutions are acceptable.
10. Following completion of chemoradiation, a baseline MRI scan must be obtained at an enrolling institution according to protocol parameters for determination of continuing eligibility. Determination of continuing eligibility in the context of possible pseudo-progression will aided by the use of dynamic contrast susceptibility imaging **(Figure 5** and **Section 14.5)**.
11. Following tumor progression, off-study medication review is limited to new anti-cancer drug regimens and Optune therapy.
12. Documentation of adverse events occurring from the date the participant completes the first VP dose until 30 days after the last intervention or a new treatment is started, whichever occurs first. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study treatment is suspected.
13. HLA: low resolution panel for HLA-A* haplotypes is to be performed locally as part of the screening evaluation. HLA status is not used for eligibility.
14. Patients are to be instructed to check injection site for up to 48 hrs post injection: staff to call within 3 to 5 days to document any reaction (see Section 15.5.5).
15. Off-study patients will be contacted by phone every 8 weeks (±2 weeks) to determine survival and subsequent cancer treatments administered.
16. TMZ administered on days 1 through 5 of 28-day cycles.
17. Vital signs to include oral or temporal (forehead) temperature, respiratory rate, blood pressure and pulse rate.

18. Height is only required at screening visit; weight only thereafter.
19. Repeat brain MRI, as assessed by the RANO criteria (-3 to -10 days from each VM visit); any brain MRIs obtained after randomization for standard of care will be collected and submitted to central imaging.
20. Brain assessment is not required if one was obtained in the previous 45 days.
21. Focused neurologic exam will be completed at the discretion of a treating physician based on symptoms.
22. UA to be completed at screening and when clinically indicated only.
23. Immunological assessments are described in Section 18.4.17.1.
24. Include INR, PT, and aPTT
25. Coagulation parameters INR, PT, and PTT will be collected at maintenance vaccine doses 1, 4, and 8.
26. This is a symptoms directed physical exam
27. Immune profiling (PBMCs and ADA) on TMZ Cycle 1 only

Appendix D – NCI Common Terminology Criteria for Adverse Events

View the NCI-CTCAE v5.0 criteria electronically at the following website:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/ (CTCAE_v5.0_2017-11-27.xls)
The study manual includes a copy of the NCI-CTCAE.