Supplement: Protocol 020221 and SAP

To

Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination in Patients with Newly Diagnosed and Recurrent Glioblastoma: A Phase 3 Prospective Externally Controlled Cohort Trial

This supplement contains the following items:

1) The SAP (v1.0) that governs all analyses for this clinical trial
2) The final clinical trial protocol (v7.0),
3) The original trial protocol (v4.0),
4) A global overview of protocol changes;

QUANTICS Biostatistics

Phase III Clinical Trial Evaluating DCVax®-L, Autologous Dendritic Cells (DC) Pulsed with Tumor Lysate Antigen, for the Treatment of Glioblastoma Multiforme (GBM)

Northwest Biotherapeutics

Study ID: 020221

STATISTICAL ANALYSIS PLAN

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Sponsor Name:	Northwest Biotherapeutics
Protocol Number:	Study ID: 020221
Protocol Title:	Phase III Clinical Trial Evaluating DCVax®-L, Autologous Dendritic Cells (DC) Pulsed with Tumor Lysate Antigen, for the Treatment of Glioblastoma Multiforme (GBM)
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I confirm that I have reviewed this document and agree with the content.

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Contents

Abbreviations

ATC	Anatomical therapeutic chemical
BMI	Body mass index
BP	Blood pressure
CD8	Cluster of differentiation 8
cPD	Confirmed progressive disease
cPFS	Confirmed progression-free survival
CPI	Checkpoint inhibitor
CS	Conditional survival
CTCAE	Common terminology criteria for adverse events
DC	Dendritic cells
EGFR	Estimated glomerular filtration rate
GBM	Glioblastoma multiforme
HR	Hazard ratio
IDH-1	Isocitrate dehydrogenase 1
IPD	Individual patient data
ITT	Intention to treat
IWRS	Interactive web response system
KM	Kaplan Meier
KPS	Karnofsky performance status
MAIC	Matching-adjusted indirect comparisons
MedDRA	Medical dictionary for regulatory affairs
MGMT	O6-methylguanine DNA methyltransferase
mOS	Median overall survival
NWBT	Northwest Biotherapeutics, Inc.
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression free survival

PP	Per protocol
PsPD	Pseudo-progressive disease
PT	Preferred term
PTEN	Phosphatase and tensin homolog
RPA	Recursive partitioning analysis
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
STC	Simulated treatment comparisons
TEAE	Treatment-emergent adverse event
TMZ	Temozolomide
TTF	Tumor treating fields
TTP	Time to progression of disease
uPD	Unconfirmed progressive disease
uuPD	Ultimately unconfirmed progressive disease
WHO	World health organization

Executive summary

This statistical analysis plan (SAP) is intended to serve as the roadmap for evaluating data (Trial Data) acquired in the Phase III clinical trial of Northwest Biotherapeutics, Inc. (NWBT) DCVax®-L autologous dendritic cells (DCs) pulsed with tumor lysate antigen, as adjuvant therapy to standard primary treatments in patients with newly diagnosed and recurrent glioblastoma multiforme (GBM), Protocol No. 020221, v7.0 (the Protocol or the Trial). This Trial is still ongoing at this time, in follow-up of the study subjects.

This is the first SAP that has been submitted for the Trial, and it is being submitted prior to Data Lock and unblinding of the study results. This SAP has been jointly developed by three independent biomedical/clinical trial statistical experts. The SAP describes our methods for analysing the Trial Data and the impact of DCVax®-L on the course of disease as accurately as possible with endpoints as described below, in accordance with scientific developments that have emerged since inception of the trial.

The original Protocol primary endpoint was to compare progression-free survival (PFS) of the Trial treatment arm with a placebo cohort. The original Protocol secondary endpoint was to compare overall survival (OS) of the trial treatment arm with the placebo cohort. However, two major real-world developments took place during the course of the Trial:

- Scientific appreciation of the phenomenon of pseudo-progression advanced, highlighting the virtual impossibility of distinguishing radiation-induced oedema, and vaccine-induced immune-cell infiltration and/or inflammation, from true disease progression. Until a broadly accepted definition of this distinction becomes feasible and is settled in the field, the subjectivity of PFS determinations suggests that the Trial data should be evaluated by a more objective endpoint, which is OS (below); and

- Such a large percentage of patients made use of the crossover option in the Protocol that the original control arm became substantially depleted and insufficient for OS analyses within the Trial. When the Trial began in 2007, per the demand of investigators and patients it was necessary to include a crossover option in the Protocol in order to recruit and retain patients. This crossover option allowed patients from both the DCVax®-L arm and the control arm of the Trial to receive DCVax®-L treatment following progression (recurrence), while they and all other parties (including the Sponsor and investigators) remained blinded as to what treatment they received before crossover. Approximately 90% of all patients in the Trial made use of this crossover, resulting in the substantial depletion of the control arm.

These two key developments require corresponding adaptation of the methodology for evaluating the Trial data, specifically:

(a) designating survival (OS) as the trial's primary endpoint and first secondary endpoint--as survival is the patients' ultimate goal--while also retaining the original progression-free survival (PFS) criteria as an additional secondary endpoint, to the extent PFS may ultimately be ascertained from analysis of the Trial Data; and

(b) replacement of the Protocol placebo control cohort with a large, closely matched, independently chosen external control group—in each case as described below.

- Endpoints: The SAP (Section 1.2) adopts the following endpoints as a basis for demonstrating efficacy:
    - ***Primary Endpoint: OS*** relative to external controls.
    - ***First Secondary Endpoint: OS following recurrence***, relative to external controls; and
    - ***Additional Secondary Endpoints***: To the extent demonstrably ascertainable from analysis of the Trial Data, confirmed PFS, and original Protocol endpoints PFS and OS.

- External Controls: Depletion of the Protocol placebo cohort is addressed in this SAP by comparing primary and secondary endpoint results in the Trial treatment arm with external control cohorts, consistent with the FDA's December 2019 Draft Guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products [1].

  The identification of appropriate external controls was done through a systematic literature search which has been conducted by the independent expert firm, York Health Economics Consortium, UK. This independent expert analysis was checked and confirmed with a panel of independent neuro-oncology experts who were not involved in the Trial. In addition, the statistical analysis includes methodologies to ensure matching of these identified external controls to the DCVax®-L trial population based on known prognostic factors, applied by independent statisticians.

Section 1: Introduction

Glioblastoma (GBM) is an orphan disease, and is the most lethal form of primary brain cancer. Patients suffer seizures, cognitive impairments and motor impairments. Survival times are very short: with standard of care (surgery, 6 weeks of radiation and concomitant chemotherapy, followed by ongoing adjuvant chemotherapy), median patient survival is only a little over a year. Long-term survival is virtually unknown, with typical 5-year survival rates of only 2-3%. Furthermore, GBM natural history is strikingly consistent. For example, in 5 large clinical trials of GBM treatments over the past decade, with 1,366 patients in the control arms of those trials who received standard of care treatment, those patients had a median survival of 16.5 months, with a 95% confidence interval of 16.0 – 17.5 months (see Section 8.1.3).

These consistent and grim survival outcomes have not significantly changed in 50 years. In 2005, concomitant and adjuvant chemotherapy with temozolomide (TMZ) was approved based on adding 10 weeks of survival, extending median overall survival (mOS) from 12 months to 14.5 months (Stupp et al. 2005) [2].

The biology of GBM poses great difficulties for treatments. GBM is one of the most genetically heterogeneous cancers. The Cancer Genome Atlas Research Network found that in tumor tissue samples from just 300 GBM patients, there were over 20,000 different somatic gene mutations. In addition, GBM is not a highly immunogenic tumor. Hence it is difficult to obtain a response to immunotherapy in GBM.

In the 15 years since TMZ was approved for GBM, scientific knowledge about GBM has advanced greatly. Today, many prognostic factors are well known (e.g., MGMT gene promoter status, IDH mutation status, age, extent of resection, performance status, etc.) and molecular sub-types of GBM have been identified and analyzed [3]. However, hundreds of clinical trials testing a wide range of diverse treatments have failed to achieve meaningful extension of survival. A survey of the trials conducted over more than a decade following TMZ approval (2005-2017) found that, out of 417 clinical trials involving 32,000 patients, there were only 16 Phase III randomized trials and only 1 of those trials was found to extend survival or provide other material benefit [4]. In the last 2 years, more Phase III clinical trials for GBM were reported, some including treatment with checkpoint inhibitor drugs (CPI), and all of these Phase III trials also failed to extend survival.

The only two new treatments approved for GBM in the 15 years since approval of TMZ in 2005 were both approved for commercial use with *no* extension of survival. The first is Bevacizumab, which received accelerated approval followed by full approval based on progression-free survival and improvement of quality of life, but no improvement in survival [5]. The second is the Optune tumor treating fields (TTF) device which was approved for recurrent GBM based upon non-inferiority with standard of care followed by a label extension to newly diagnosed GBM, based on prolongation of progression free survival and overall survival [6].

For all of the foregoing reasons, there is a severe unmet medical need for new and better treatments for GBM that extend survival. This Phase III trial of DCVax®-L, with an intent to treat (ITT) population of 331 patients, is one of the last remaining Phase III trials for GBM that is currently still active. To better analyze the data based on the current scientific advances and the recent understanding of the GBM biology, its natural history and response to therapy over the past 13 years, we have developed this SAP.

The design of this SAP has been developed by multiple independent experts, and reviewed by independent, leading neuro-oncology experts who were not involved in the Trial, and all of the analyses called for under this SAP will be carried out by independent experts. This SAP was developed prior to data lock and unblinding of the Trial data.

1.1 Study design

The 020221 clinical trial was designed as a randomized, placebo-controlled, double blinded, multi-center, multi-national Phase III trial (the "Trial"). Subjects with newly diagnosed GBM (confirmed through independent central pathology review) having surgically accessible, unilateral tumor for which surgical resection is indicated, with intent to perform a gross total or near gross total resection, were eligible to be considered for enrolment.

Following standard of care therapy, consisting of surgical resection followed by external beam radiation and concurrent chemotherapy (temozolomide), subjects not showing signs of early recurrence are randomized to either DCVax®-L or Placebo with a randomization ratio of 2:1. Subjects are stratified for randomization by site and by MGMT methylation status (methylated or not methylated).

All subjects in the Trial are followed for the collection of data on progression and survival.

A crossover option was included in the Trial design on demand of patients and investigators, and was necessary to enable recruitment and retention of patients when the Trial began 13 years ago in 2007. The crossover option in this Trial is different from various other crossover designs sometimes used in other trials. In this Trial, all subjects -- from both arms of the Trial -- who have tumor progression (recurrence) have the option to receive DCVax®-L treatment post-progression. In addition, all subjects who do receive DCVax®-L after progression receive it on the same basis (same treatment schedule, etc.), regardless of which treatment arm of the Trial those patients were in before progression. Of crucial importance: under this design, all parties remain blinded as to which treatment the subjects received before progression (the patients, investigators and sponsor all remain blinded).

The large number of patients who elected to cross over depleted the control arm in the Trial. About 90% of all patients in the ITT population crossed over, including most of the patients in the original control arm. This depletion of the control arm left too few patients for effective comparisons within the Trial.

In addition, even if comparisons within the Trial were still feasible, they could lead to misleading results. In patients who were originally assigned to the control arm and who receive DCVax®-L only

after they cross over post-progression, if these patients experience survival extensions there may be little difference in the survival curves between the two arms of the trial. Analyses focused on the difference in survival curves between the two arms in the Trial may give a fundamentally inaccurate picture by making it appear that there are no clinical effects from DCVax®-L treatment while, in reality, the lack of difference between the survival curves may mean the opposite: i.e., that there are clinical effects from DCVax®-L treatment at both the newly diagnosed stage and the post-progression (recurrent) stage of the disease.

The first secondary endpoint under this SAP tests the question of whether the time from progression (recurrence) until death may still be longer than with standard of care if a patient only starts receiving DCVax®-L at crossover. That endpoint evaluates the effect of starting DCVax®-L treatment at the stage of recurrent disease, when the control arm patients cross over.

The second secondary endpoint under this SAP compares survival in the original treatment arm with survival in the original control arm of the Trial. If there is little or no beneficial effect on survival from starting DCVax®-L treatment after progression and crossover, then the comparison of the original treatment and control arms may still provide an accurate picture despite the crossovers.

In light of the depletion of the control arm, and the potentially misleading picture from comparison of the survival curves between the two arms of the Trial, this SAP uses external controls who only received Standard of Care.

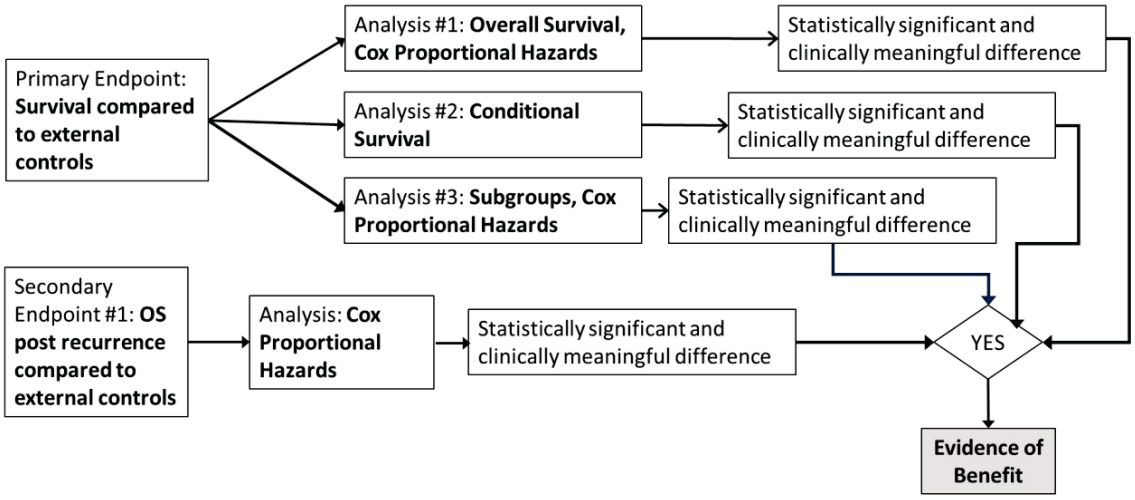
The identification of the most appropriate external controls from other clinical trials in newly diagnosed GBM, based upon comparable patient populations, time period of trial conducted, extent of resection and standard of care RT/TMZ treatments consists of a structured literature search and has been conducted by the independent expert firm, York Health Economics Consortium, UK (see Appendix A). This independent expert analysis was checked and confirmed with a panel of leading, neuro-oncology experts who were not involved in the Trial. In addition, the statistical analyses include methodologies to ensure appropriate matching of these identified external controls to the DCVax®-L trial population based on known prognostic factors, applied by independent statisticians.

To support the first secondary endpoint for survival analysis in recurrent GBM, a systematic literature search was also conducted similarly, to identify the most appropriate external controls from clinical trials in recurrent GBM, based upon comparable patient populations and the time period of the trial conducted (see Appendix B).

1.2 Study endpoints

This SAP analyses overall survival (OS) in three ways, with each compared to external controls. Each of these three analyses is clinically important. Each of these analyses is separate, with a portion of the statistical alpha assigned to each of them. Specific analytical methods are described in Section 8 of this SAP. The analyses are shown below.

Figure 1: Primary Endpoint and Secondary Endpoint #1: OS Compared With External Controls



1.2.1 Primary endpoint: OS compared with external controls – 3 analyses

Analysis #1: Overall survival in the whole patient population: This analysis will evaluate the overall survival curves and median survival for all of the patients in the Trial (both ITT and PP populations). This analysis will compare the survival times of the 232 patients initially randomized to DCVax®-L to the selected external controls. The comparisons will include the following:

- an overall comparison of the 232 patients to all external control patients, pooled;
- a matching-adjusted indirect comparison (MAIC) that takes into account the distribution of prognostic factors between the 232-patient DCVax®-L trial population and the external controls, pooled;
- a MAIC of the 232 patients to the control patients of each individual external control trial.

All comparisons will include an overall curve comparison, as well as comparisons of survival percentages at certain time points (so-called milestone analyses).

Analysis #2: Conditional survival -- the "long tail": This analysis will evaluate specifically the "long tail" of survival in patients treated with DCVax®-L in this Trial. With immunotherapies, one of the features most focused upon and considered most important clinically is their capability to deliver greatly extended survival in a percentage of patients. This analysis will apply an established statistical methodology – conditional survival – to evaluate the survival tail in this Trial separately from the larger picture. This methodology will evaluate all of the survival data relating to patients who survived beyond a specified time threshold. (This time threshold is the "condition" or trigger of the analysis). By analysing all of the data from the time threshold onwards, this methodology evaluates the whole survival tail and provides a more complete and representative assessment than a landmark analysis which would only evaluate the status of the survival tail at a specific time point.

Analysis #3: Survival in pre-specified sub-groups: It has become well recognized that GBM patients may be categorized into distinct sub-groups based upon certain patient characteristics and/or tumor characteristics, and these distinct sub-groups have materially different survival with GBM. Such

characteristics include the methylation status of the MGMT gene in the tumor, IDH mutation status, extent of surgical resection of the tumor, and others. As explained above, in this SAP a portion of the statistical alpha is separately assigned to analysis of pre-specified sub-groups. This alpha will be applied to the first sub-group analysis. After the first one, additional sub-group analyses will be conducted in a hierarchy – i.e., each successive sub-group analysis after the first one will be reached if the one before it is positive. The first sub-group analysis will be survival in patients with methylated MGMT gene. Thereafter, additional analyses will include, minimal residual disease, age <65, significant residual disease, unmethylated MGMT, and age ≥ 65.

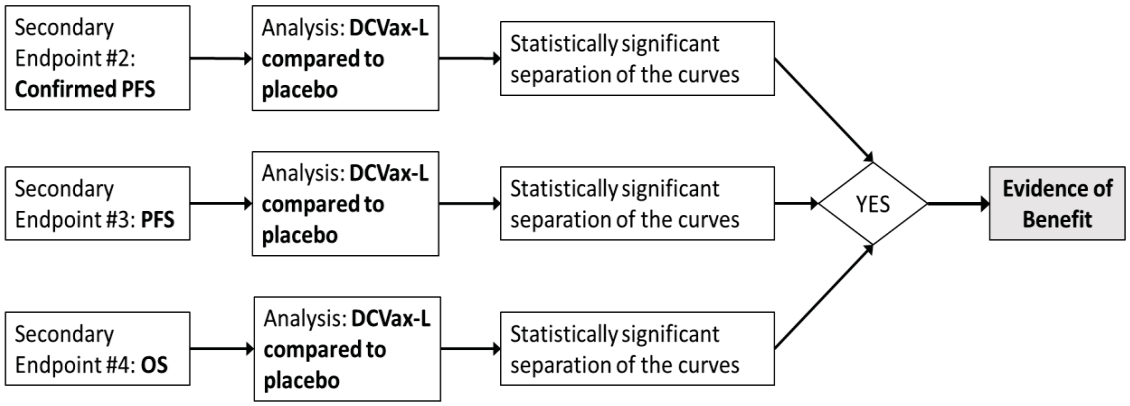
1.2.2 Secondary endpoint #1: Post-progression OS compared with external controls

Secondary Endpoint #1 measures survival (OS) post-progression in patients who were initially randomized to the placebo arm of the Trial, received only standard of care treatment until progression (recurrence), and then started receiving DCVax®-L treatments following recurrence. These recurrent GBM patients comprise an important part of the data set from this Trial. These patients will be compared with external control groups from studies in recurrent GBM. Those studies have been selected by independent experts in the same manner as the studies for external controls for the Primary Endpoint. Specific analytical methods are described in Section 8 of this SAP.

1.2.3 Additional secondary endpoints: PFS and OS comparing arms within trial

After the Primary Endpoint and Secondary Endpoint #1 are analyzed in comparison with external controls, as described above, several additional Secondary Endpoints will be analyzed in a comparison between the two arms or cohorts within the Trial. These analyses are shown below.

Figure 2: Additional Secondary Endpoints: Comparisons Within Trial



Secondary Endpoint #2: Confirmed Progression Free Survival (cPFS) - Comparison between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

As explained above, it has become well recognized that pseudo-progression (PsPD) may occur in a substantial percentage of patients (e.g., up to 30% of brain cancer patients). Traditional methods of analysing progression tend to rely upon one set of MRI scans at the time when progression or

pseudo-progression appears. It has been observed that pseudo-progression (e.g., edema) may subside over time while real progression will not. So, analysing a series of MRI scans and other measures in order to confirm progressive disease should help obtain a more accurate assessment of real vs. pseudo-progression.

For purposes of the Secondary Endpoint #2, Confirmed Progressive Disease (cPD) is defined as initial disease progression determined through independent review (unconfirmed PD), AND also either (i) a new lesion or (ii) any one of the following criteria (modified iRANO criteria):

- A further 25% increase or greater in the sum of bi-perpendicular diameters of enhancing tumor, occurring at least 4 weeks after the initial event of PD/PsPD;
- Significant increase in T2/FLAIR non-enhancing lesion attributable to tumor growth;
- Death (all deaths are counted as events).

A secondary analysis will, in addition to the MRI findings, take into account the clinical status of the patient, as follows:

- Non-temporary increase in steroid dose >2 mg/day not associated with the unconfirmed PD event;
- Significant clinical decline not attributable to other causes;

Secondary Endpoint #3: Progression-Free Survival (PFS) – Comparison between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

PFS as described in the original trial protocol uses modified Macdonald criteria to define disease progression and compares PFS between subjects randomized to DCVax®-L to those randomized to placebo within the Trial. The MacDonald criteria are no longer used in the field and cannot distinguish between actual disease progression and pseudoprogression. This endpoint will therefore likely be confounded due to pseudo-progression (PsPD) events being counted as PD. Such PsPD may be due to effects of surgery and/or radiation therapy or may also be induced by the DCVax®-L vaccine (i.e., T cell infiltration). This second form of PsPD occurs frequently in subjects receiving DCVax®-L, as may be seen through case studies.

Secondary Endpoint #4: Overall Survival (OS) – Comparison between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

OS as described in the original trial protocol compares survival in subjects randomized to DCVax®-L to those randomized to placebo within the Trial. Secondary Endpoint #4 is an OS analysis on this basis. However, due to the crossover option in the trial design for all patients in both arms of the Trial, and the fact that 90% of the total patients have received DCVax®-L, this means that the majority of subjects randomized to placebo have received DCVax®-L treatment following disease progression. This will result in a potential convergence of the survival curves if there is a survival benefit conferred on these crossover subjects as a result of the DCVax®-L treatment.

Secondary Endpoint #5: Tumor Response – Comparison between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

Resection of GBM typically focuses on removing the enhancing tissue as that is supposed to be the area of active tumor growth. Incomplete resections result in residual enhancing disease post-surgery and most patients also have non-enhancing disease areas surrounding the enhancing lesion. Tumor response will use pre- and post-randomization measurements of enhancing and non-enhancing disease. Modified RANO criteria will be applied per Cloughesy et al. [7], allowing for evaluation of non-measurable disease to determine response rates.

1.2.4 Exploratory endpoints

The following exploratory (tertiary) endpoints were defined in the original clinical trial protocol:

- To compare the following between subjects in the DCVax®-L arm and subjects in the placebo arm within the Trial:
- Immune profiles in the peripheral blood that may be predictive of response/non-response to immunotherapies
- Decline in physical functioning, measured by Karnofsky Performance Status (KPS) evaluation
- Time to progression of disease (TTP)
- Survival at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months
- Times to PFS, OS and TTP, measured from initial surgery.
- To evaluate further the safety profile of DCVax®-L.

1.3 Sample size

1.3.1 Sample size for PFS

The sample size calculations were based on PFS. Table 1 shows the assumptions made.

Table 1: Assumptions Made to Support Sample Size Calculation

Ratio between the treatment arm and the placebo arm	2:1
Accrual period	36 months
Time to accrual of 50% of subjects	22 months
Follow up period	5 months
Loss to follow up, per arm per month	1%
Median PFS for placebo arm	7 months
Test for comparing PFS between arms	Log rank
Type I error	$\alpha = 0.01$, one sided

To achieve 84% power when median PFS is 11 months in DCVax®-L-treated subjects, 348 subjects would be required in total: 232 in the DCVax®-L arm and 116 in the placebo arm. The corresponding total number of events required is 248.

1.3.2 Sample size for OS

The implication of this sample size of 348, accrued as described above, for the OS endpoint is as follows. We assumed median OS of 17 months among subjects in the placebo arm, and set the type I error rate for this analysis to 0.025, one-sided. To detect the expected benefit of 8.3 months' increase in median OS (to a median of 25.3 months) in the DCVax®-L arm would require an extension of the follow up time to 36 months after completion of enrolment. Then the power of the log-rank test is approximately 80.5%. The corresponding number of events is approximately 233.

1.4 Interim analysis

The original trial protocol specified the following interim analyses:

Two interim analyses for PFS were to be performed. The first was to occur after approximately 60% of the expected PFS events (i.e. 149 events) had occurred; the second after approximately 80% of the expected PFS events (i.e. 198 events) had occurred. In practice, one interim analysis was conducted. Group sequential methods were to be used for these analyses to control the Type I error rate. Critical values for interim testing were to be calculated using the method of Lan-DeMets and an O'Brien-Fleming spending function. The significance levels at the interim and final analyses were to be calculated using the O'Brien-Fleming alpha spending function:

$$\alpha_1(t^*) = 2 - 2\,\Phi\left(\frac{Z_{\frac{\alpha}{2}}}{\sqrt{t^*}}\right)$$

where α=0.05 is the overall (2 sided) significance level and t^* is the proportion of the total events that occurred until the time of the interim analysis.

1.5 Randomization

Randomization was performed using an interactive web response system (IWRS) and was initiated upon a randomization request form submitted by the trial site followed by review of all eligibility criteria. The randomization was stratified by site and by MGMT methylation status (methylated/ unmethylated), and used a permuted block design with a fixed block size.

1.6 Additional subject cohorts included in the study

The subjects enrolled into the study according to the inclusion and exclusion criteria defined in the study protocol (the ITT population) will be referred to as the 'Main investigational cohort'. During the course of the study, two further cohorts outside of the ITT population were added: an 'Informational cohort' and a 'Pseudo-progression cohort'.

1.6.1 Informational cohort

Subjects not eligible for randomization were offered an opportunity to participate in a separate compassionate use treatment cohort since at time of screening for enrolment and randomization,

the personalized DCVax®-L product had already been manufactured. These subjects are referred to as the "Informational Cohort" or "Information Arm" and are not part of the main study.

1.6.2 Pseudo-progression cohort

A group of subjects, also not included in the 331 patients main study, who already had evidence of possible progressive disease at baseline (and hence were ineligible for the trial), but after 10 weeks' post radiation therapy did not show signs of real progression based on MRI, were assigned to the 'Pseudo-progression cohort'. Within that cohort, patients were randomized at a ratio of DCVax-L to Placebo of 2:1.

1.7 Genomic/genetic outliers

New molecular and genetic information that has emerged in the field may be of relevance in interpreting the data emerging from this trial. Such data include information on IDH1 mutational status and 1p19q chromosomal deletions. Patients with these mutations are generally considered to suffer from a lower grade glioma, with extended time to progression and longer survival times. These forms of glioma had not been identified in 2007 at the time the study was initiated, and it is possible that some patients randomized into the study may have these molecular subtypes, despite the histological confirmation of GBM. Sensitivity analyses for the Trial endpoints will include analyses on patients who do not have either one of these genetic variations.

Section 2: Analysis sets

2.1 Study cohorts

The total study population comprises three cohorts of subjects:

- Main investigational cohort: all subjects satisfying the protocol eligibility criteria (the ITT population)
- Pseudo-progression cohort
- Informational cohort

2.2 Study populations

The following analysis sets will be defined for analysis:

Intention to treat (ITT) population

All subjects in the Main Investigational Cohort randomized to the DCVax®-L or placebo arms.

Data will be analyzed for efficacy endpoints according to the subject's randomized allocation.

Per Protocol (PP) population

All subjects in the ITT population with the exception of those:

- who did not receive DCVax®-L [or did not receive full treatment] because sufficient vaccine could not be produced;
- who did not receive any DCVax®-L [or did not receive full treatment] for other reasons;
- with other major protocol deviations (as determined at blinded data review), including those who did not receive their randomized treatment at all, for whatever reason.

Subjects will be analyzed for efficacy endpoints according to the first study treatment they received.

All analyses conducted for the primary and secondary endpoints will be repeated for the PP population.

Safety population

All subjects in all three cohorts who received at least one immunization with DCVax®-L or placebo. Subjects will be analyzed for safety endpoints according to the treatment they actually received. Subjects will be analyzed in aggregate as well as separately by cohort. Subjects will be analyzed for efficacy endpoints according to their randomized allocation.

2.3 Use of study populations

Demographics and baseline characteristics will be reported separately for:

- ITT population
- PP population

- Pseudo-progression cohort
- Informational cohort

Efficacy data will be reported separately for:

- ITT population
- PP population
- Pseudo-progression cohort
- Informational cohort

Note:

1. The conditional survival endpoint is calculated in patients reaching the chosen threshold.
2. Subgroup analyses will also be conducted.
3. The efficacy analysis for the Informational cohort will not be comparative, as there is only one arm, and will only include descriptive statistics.

Safety data will be reported for the Safety population.

2.4 External comparator populations

Systematic literature reviews have been conducted by independent experts, followed by consultation with neuro-oncology experts, to identify relevant studies in newly diagnosed GBM and in recurrent GBM respectively, to provide comparator control populations as described above. Two separate reports (one for newly diagnosed GBM and one for recurrent GBM), detailing search terms, databases searched and all other relevant details, are provided as Appendices.

Section 3: Endpoints

3.1 Study endpoints based on survival and progression

Table 2 summarises the endpoints defined by survival and progression.

Table 2: Endpoints

Endpoint	*Populations*	*Model*	*Estimator*	*Multiplicity[1]*
Primary: DCVax®-L Study *020221[2] vs external controls[3] in newly diagnosed GBM*				
OS	ITT & PP	Cox PH[4]	Hazard ratio; landmarks	α-exhaustive extension of the fallback [8] procedure, plus hierarchy
CS[5]	ITT & PP		Hazard ratio	
OS	ITT & PP subgroups		Hazard ratio; landmarks	
Secondary: DCVax®-L Study *020221 crossover cohorts vs external controls[6] recurrent GBM*				Hierarchy
OS	Placebo crossover cohort	Cox PH	Hazard ratio; landmarks	
Secondary: Internal to Study *020221*				
cPFS[7]	ITT & PP	Cox PH	Hazard ratio; landmarks	
PFS	ITT & PP	Karrison procedure for log rank test	Hazard ratio; landmarks	
OS	ITT & PP		Hazard ratio; landmarks	
Sensitivity analyses: Internal to Study *020221*				
OS	ITT & PP	Cox PH	Hazard ratio; landmarks	
PFS	ITT & PP		Hazard ratio; landmarks	
OS	ITT & PP biomarker subgroup[8]		Hazard ratio; landmarks	
PFS	ITT & PP biomarker subgroup		Hazard ratio; landmarks	
Exploratory: Internal to Study *020221*				
TTP[9]	ITT		Hazard ratio; landmarks	

[1] α 5% 2 sided overall; accounting for interim analysis, final analysis to be conducted at α 2.409% 1 sided
[2] Subjects randomized to DCVax®-L
[3] Control arms from studies in newly diagnosed GBM identified in systematic literature review by independent experts, confirmed with independent neuro-oncology experts and further matched through MAIC
[4] Analysis based on reconstructed IPD from external studies; if real data available then covariates included as available
[5] Survival conditional on OS ≥ Observed median survival in Subjects randomized to DCVax®-L
[6] Control arms from studies in recurrent GBM identified in systematic literature review by independent experts, confirmed with independent neuro-oncology experts and further matched through MAIC
[7] Confirmed PFS
[8] ITT population excluding: IDH-1 mutated and chromosome 1p19q co-deletions
[9] Time to Progression

3.1.1 Overall survival

For the Primary Endpoint, analyses #1 (ITT Population) and #3 (Pre-Specified Sub-Groups), OS will be calculated from the date of randomization to the date of death due to any cause. If a subject is not known to have died at the date of database lock, that subject will be censored at the date the subject was last known to be alive. For these Primary Endpoint analyses, OS for subjects randomized to DCVax®-L will be compared to closely matched, independently determined external controls.

For Secondary Endpoint #1 (Post-Progression OS), OS will be calculated from the date of progression to the date of death due to any cause for subjects originally randomized to placebo who received DCVax®-L after crossover. If a subject is not known to have died at the date of database lock, then the death for that subject will be censored at the date that the subject was last known to be alive. For these Post-Progression OS analyses, the subjects who received DCVax®-L after crossover will be compared to matched external controls obtained from trials in recurrent GBM.

For Secondary Endpoint #4 (OS in the ITT population), OS will be calculated from the date of randomization to the date of death due to any cause or date the subject was last known to be alive in the same manner as for the Primary Endpoint analysis #1, except that the OS for subjects randomized to DCVax®-L will be compared to Within-Study controls (i.e. subjects randomized to placebo).

3.1.2 Conditional survival

For Primary Endpoint analysis #2 (Conditional survival or CS), survival will only be evaluated for subjects known to have survived to at least the observed median (M months OS) for subjects randomized to DCVax®-L. CS will be calculated from M months after the date of randomization to death due to any cause. If a subject is not known to have died at the date of database lock, the date the subject was last known to be alive will be used to calculate CS and will be considered censored [9].

Published data from other trials include OS at various time points and include Kaplan-Meier (KM) survival curves. The KM curves will be digitized and individual survival data will be derived from the digitized KM curves. In addition, access may be obtained to original data sets from some other trials. CS for subjects randomized to DCVax®-L in the Trial who survived to at least the observed median will be compared to matched external controls comprised of subjects who survived to at least the same time point (M months) in the other trials which have been selected by independent experts, confirmed with independent neuro-oncology experts and further matched through MAIC, pursuant to this SAP to serve as the comparison trials.

cPFS for subjects randomized to DCVax®-L will be compared to within-Study controls (i.e. subjects randomized to placebo).

3.1.3 Confirmed progression-free survival

Confirmed PFS (cPFS) will be measured from the date of randomization to the date of confirmed progressive disease (cPD; see section 1.2.2, Appendix C) or death. An initial determination of

progression will be made in the same manner as for PFS (see sections 1.2.2, 3.1.4 and Appendix C): these events will for this analysis be qualified as 'unconfirmed progression' (uPD) events. Subsequent review of these events will then determine whether they can be confirmed, or not, and only events that are subsequently determined to be confirmed progression will be counted as events for the cPFS endpoint. Events initially classified as uPD which are not subsequently confirmed will be censored.

cPFS for subjects randomized to DCVax®-L will be compared to cPFS for withhin-Study controls (i.e. subjects randomized to placebo).

3.1.4 Progression-free survival

PFS is defined as the time from randomization until objective demonstration of tumor progression or death, whichever occurs first [10]. If neither tumor progression nor death are known to have occurred by the date of database lock, the date the subject was last known to be alive and progression-free will be used to calculate PFS, which will be considered censored.

When data points, especially in regards to radiographic imaging data, are missing, strong efforts will be made to obtain the missing study information. In spite of these efforts, there may be missing data regarding assignment of primary and secondary endpoints. Detailed rules for the definition of progression-free survival (modified Macdonald criteria) are provided in Appendix C.

Within-Study controls are used for this endpoint.

3.1.5 Time to progression

Time to progression (TTP) is defined as the time from randomization to disease progression (per modified Macdonald criteria determined by independent ICON Medical Imaging review). For patients who die before experiencing progression, TTP will be censored at the date of death. Within-Study controls are used for this endpoint.

3.2 Other endpoints

3.2.1 Immunostimulatory response

A subject will be considered a responder if any of the following conditions holds:

- T cell proliferative response to DCVax®-L shows a stimulation index of 2 or greater;
- A greater than 3-fold increase in CD8+ cells staining with tumor antigen tetramers;
- An ELISPOT response exceeding background signal by at least 2 standard deviations. The background signal will be based on the level of response in patients randomized to placebo.

3.2.2 Physical functioning

- Time from date of randomization to a 10-point decline in KPS will calculated.
- Time from date of surgical resection to a 10-point decline in KPS will calculated.

3.2.3 Endpoints measured from surgery

The primary and secondary endpoints will be measured from the time of initial surgery ('is'), in addition to being measured from randomization as described above:

- isOS
- isCS
- isOS – sub-groups
- isOS – post-progression
- iscPFS
- isPFS
- isTTP

These endpoints are defined the same as for OS, CS, OS (sub-groups), OS (post-progression), cPFS, PFS, OS and TTP but with the time interval measured from initial surgery in place of randomization.

3.2.4 Tumor response

Subjects deemed to be responders (as defined in section 1.2.3) will be identified according to RANO or iRANO criteria, modified per Cloughesy et al. [7].

3.2.5 Ultimately unconfirmed progression

For the cPFS (confirmed PFS) endpoint, events that have been preliminarily identified as disease progression by MRI (uPD events) are classified as cPD events if subsequent scans or medical review demonstrate further progression. The remaining uPD events will be classified as uuPD events, for ultimately unconfirmed disease progression. These uuPD events will by default include events that are not reflective of actual disease progression and will therefore contain a large proportion of the pseudo-progression events, including those induced by DCVax®-L vaccination, that may have occurred in this study.

A KM plot of the percentage of subjects free of uuPD events versus time by treatment arm is intended to aid in the interpretation of the influence of vaccine-induced, pseudo-progression, if any, on the analysis of the primary and secondary endpoints. One example is that an increase incidence in uuPD events over time in the DCVax®-L treatment group relative to the control group could possibly be an indication of the presence of vaccine-induced, pseudo-progression in the analysis of OS, cPFS and PFS.

Section 4: General points for statistical analysis

4.1 General considerations

All summaries and listings will be presented by treatment group.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using numbers and percentages. The number of missing values will be presented in summary tables.

Unless otherwise specified, the estimated mean and median for a set of values will be reported to 1 more decimal place than the original values, and standard deviations will be reported to 2 more decimal places than the original values. The minimum and maximum will report the same number of decimal places as the original values. Percentages will be displayed with 1 decimal place; percentages will not be presented when the number is zero; 100% will be presented as an integer.

All data will be listed. Data listings will be presented by treatment group.

All statistical analyses will be performed using SAS® Version 9.4 [11] or STATA 15 [12].

4.2 Missing data

No imputations will be made for missing data, except in case of missing scans which are addressed in Appendix C.

Section 5: Subject disposition

The following will be tabulated over all screened subjects (the number of subjects in the screened set will be used as the denominator in the calculation of percentages):

- Number of subjects screened
- Number (% of screened) of subjects randomized into the Main Investigational cohort (ITT population)
- Number (% of screened) of subjects randomized into the Pseudo-progression cohort
- Number (% of screened) of subjects entered into the Informational cohort

Split by treatment group for the ITT population:

- Number (% of randomized) of subjects who complete the study follow-up
- Number (% of randomized) of subjects who withdraw, by reason
- Number (% of randomized) of subjects who crossed over following progression
- Number (% of randomized) of subjects in the PP population

Split by treatment group for the PP population:

- Number (% of randomized) of subjects who complete the study follow-up
- Number (% of randomized) of subjects who withdraw, by reason
- Number (% of randomized) of subjects who crossed over following progression

Split by treatment group for the Pseudo-progression cohort:

- Number (% of randomized) of subjects who complete the study follow-up
- Number (% of randomized) subjects who withdraw, by reason
- Number (% of randomized) subjects who crossed over following progression

All subjects in the Informational cohort:

- Number (% of randomized) of subjects who complete the study follow-up
- Number (% of randomized) subjects who withdraw, by reason

A CONSORT diagram will be produced.

Section 6: Demographics, other baseline characteristics, medications

Demographics and baseline characteristics such as age, extent of resection, and performance status are known prognostic factors for patients with GBM. In addition, methylation of the MGMT gene promoter is a predictive factor for response to temozolomide therapy, and other factors such as IDH-1 and -2 mutation status, 1p19q co-deletion, genetic markers such as EGFR mutations, amplification status and PTEN mutations may also contribute to outcomes in this disease. Factors such as these will be considered when interpreting the trial endpoints, as described below. All analyses and assessments will be done on both an ITT population and PP population basis, although formal claims will be made on an ITT population basis.

6.1 Demographic and other baseline characteristics

Demographics (age, gender, race), baseline MGMT status, IDH mutational status, extent of resection, and Karnofsky performance status will be summarized overall and by treatment group. Distributions of treatment group data will be compared via a t-test (age) or a chi-squared test; p values will be reported for information only, to allow an assessment of the balance between the randomized groups.

Genetic markers including EGFR and PTEN status, and chromosomal abnormalities including 1p19q deletions will likewise be summarized overall and by treatment group.

6.2 Medical history and concomitant diseases

Medical history summaries will be presented overall and by treatment group. Each subject will be counted only once in each category. Concomitant diseases will be identified as those flagged as 'ongoing' and will also be summarised separately.

In addition, oncological history will be summarised.

6.3 Prior and concomitant medications

Prior and concomitant medications will be presented for the safety population by ATC level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with numbers and percentages for each treatment group and overall. A subject who took more than one medication will be counted only once if these medications belong to the same ATC level 5 classification.

Prior medications will be defined as those medications started prior to the administration of study drug on Day 0. Concomitant medications will be defined as those medications taken following the first administration of study drug on Day 0. Hence medications started before study dosing, but continuing after, are considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

If either the start or stop date of medication is missing, the worst or most conservative case will be considered when assigning medications to categories. For a missing start date (where stop date is after date of first dose) the date will be imputed as the date of first dose; for a missing stop date the date will be imputed as the date of last dose or start date if start date is after last dose. If a partial date is recorded, the following convention will be used to assign the medication:

If a partial date is missing a start day and the month/year is the same as first dose date then use first dose date, or else '01' will be used for the day; if a start date is missing a month and the year is the same as first dose date then use first dose date, or else January will be used for the start month.

If a partial date is missing a stop day and month/year is same as the last dose date then use the last dose date, or else the last day of the given month will be used for the stop day; if a stop date is missing a month and the year is the same as last dose date then the last dose date will be used, or else December will be used for the stop month.

6.4 Current disease and therapy

The parameters that will be evaluated include but are not limited to the following:

Disease:

- Tumor size and characteristics, such as GBM subtype, histological stage of GBM, genetic, proteomic and molecular profile
- Immunoscore
- Leukocyte measures including but not limited to:
    - Absolute lymphocyte count
    - Absolute and % T cell count
    - Absolute and % CD4+ T cells
    - Absolute and % CD8+ T cells
    - Absolute and % NK cells
    - Neutrophil: lymphocyte ratio
    - T-regulatory cell count
    - MDSC count
    - TDL+ monocyte count
- Immune checkpoint and checkpoint ligand expression
- Liquid biopsy measures, including but not limited to CTCs, CTDNA, EVs and others
- Biomarkers
- Blood characteristics

Co-morbidities

Therapy:

- Extent of resection (complete/ partial and significant residual /minimal residual)
- Radiation therapy number of sessions and total dose
- Concomitant temozolomide dose per day / days

- Adjuvant temozolomide dose per day / days and months
- Number of DCVax®-L doses
- Steroid therapy dose per day / days
- Concomitant medications

Section 7: Exposure

The scheduled dosing regimen in the double-blind period comprises 10 administrations. However, some participants in the DCVax®-L treatment arm may not receive 10 immunizations due to insufficient manufacturing material (Protocol Section 3.3) or otherwise. The intended number of cells for each treatment is 2.5 million cells (two injections of 1.25 million cells). The volume of study drug for delivery of that number of cells is participant-specific (Protocol Section 8.1).

Further, all participants in both treatment cohorts whose disease progresses, as defined in Section 15.2 of the protocol, were offered a crossover option at the time of disease progression. All the participants from either arm of the trial who elected to receive DCVax®-L in the crossover, will have re-started the original 10-administration schedule using DCVax®-L, with all parties (patient, investigator, CRO and sponsor) remaining blinded to the patients' original randomized allocation.

For all subjects in both treatment cohorts, the following exposure variables will be calculated for the initial trial period and the crossover period:

- Number of DCVax®-L administrations
- Total number of cells received per administration
- Total number of cells received overall

These will be summarized as continuous variables, by treatment group and overall.

The numbers and percentages of subjects who receive at least 3 administrations, and who receive at least 6 administrations, will also be summarized as categorical variables by treatment group and overall.

Section 8: Efficacy

In the analyses described below, the following methods will be used for confidence interval calculation:

- Hazard ratio: Wald method
- Median survival: Brookmeyer and Crowley method
- Landmark survival probabilities: Hall-Wellner method (calculated on the log scale and back transformed)

8.1 Statistical methods for the analysis of the primary endpoints: comparison with external study control groups

8.1.1 Type I error for the Primary Endpoints

The overall one-sided type I error for the study was set at 2.5%. One of the two planned interim efficacy analysis was conducted in March 2015 after 56.4% of subjects had completed 6 months follow up. The O'Brien-Fleming one-sided alpha level for the final analysis (i.e. the stage 2 alpha level) is 2.409%.

Final testing for the three analyses of the primary endpoint will follow an alpha-exhaustive, fallback procedure [8].

An alpha level of 2% will be used with OS, 0.309% will be used with CS and the remaining 0.1% will be used for the analysis of OS in the pre-specified subgroups. The testing will proceed as presented in Figure 3 (below); in this way, the family-wise error rate is preserved at 2.409% for the primary endpoints.

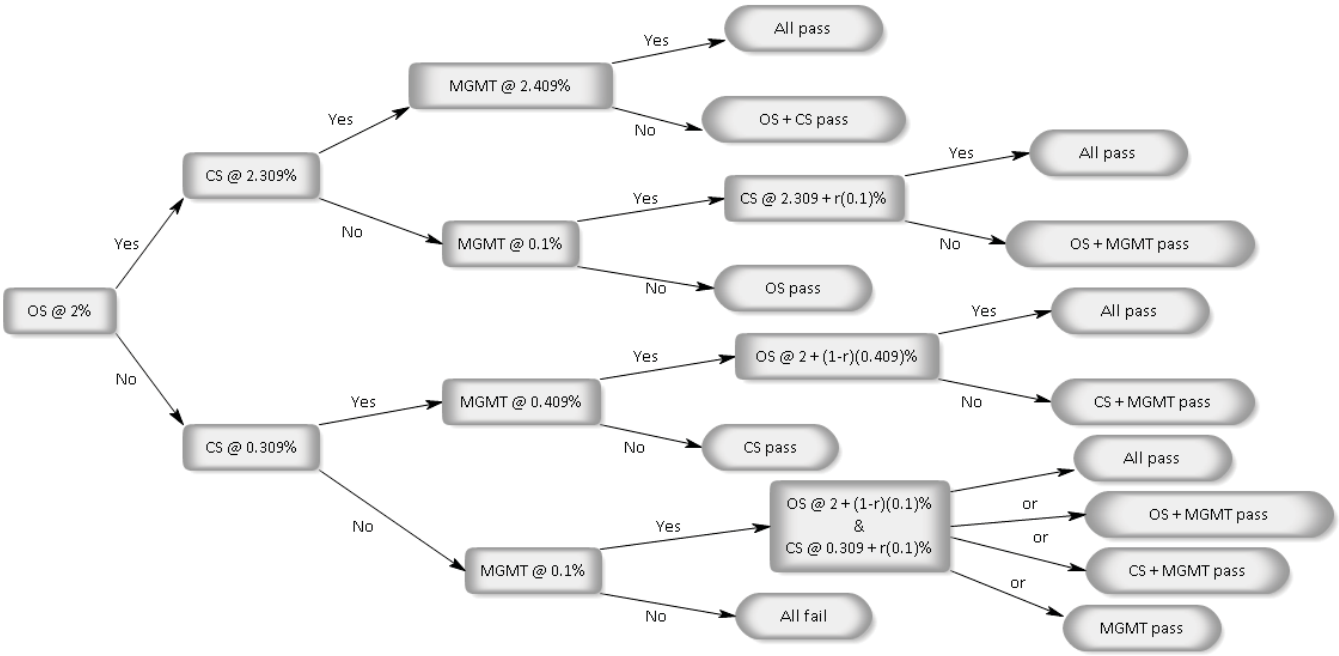
The additional pre-specified subgroup analyses will be conducted in order, at the same alpha level as for the MGMT methylated subgroup, as follows.

2. Extent of resection: Minimal residual disease
3. Age < 65
4. MGMT unmethylated
5. Extent of resection: Significant residual disease
6. Age ≥ 65

Success of the study

The significance of each of the endpoints will be tested via one-sided upper confidence limits for the hazard ratios. Figure 3 shows the possible outcomes of the study.

Figure 3: Decision tree for study success



Where $r = \frac{\alpha_2}{(\alpha_1+\alpha_2)} = \frac{0.3}{2.3} = 0.13$

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8.1.2 Threshold and methods for conditional survival

The median survival time in months, M, for all subjects randomized to receive DCVax®-L will be estimated via the Kaplan-Meier estimate of the survival function. This value will be used as the threshold for the conditional survival endpoint.

The proportional hazards assumption will be assumed to hold for CS for the DCVax®-L group and the external controls and the Cox model will be used to compare these groups. The assumption will be checked graphically.

8.1.3 External studies in newly diagnosed GBM

A systematic literature review has been conducted by independent experts to identify appropriate studies in newly diagnosed GBM to provide the external controls. This selection of studies has subsequently been reviewed by independent key opinion leaders in the field who were not involved in conducting the Trial, and has received their support. The five studies shown in Table 3 [6, 13-16], which were conducted in similar populations as in the current Phase III study, each with a control arm treated with the standard radiotherapy and temozolomide regimen, will be included. It is possible that additional studies may be added, e.g. with the goal to provide a larger population of patients with long (e.g. ≥ 4 years) follow-up times. In addition, a MAIC will be undertaken to ensure matching of the Trial subjects and the external controls.

It is recognized that each of these studies had unique inclusion and exclusion criteria, and that no single study can provide a perfectly matched control population. Nevertheless, the distribution of known prognostic factors between the enrolled patient populations reveal that these populations were similar in composition, and in fact the study outcomes are also remarkably similar: These five studies selected by the independent expert review provide 1,366 patients for the combined control group in total.

Median overall survival for these 1,366 patients is 16.5 months, with a 95% confidence interval of 16.0 to 17.5 months, demonstrating that outcome in this disease is highly consistent and predictable.

The Gilbert et al. (2014) study randomized patients 3 weeks prior to completion of chemoradiation therapy, and if that study is excluded from the analyses the outcomes of the control subjects are as follows: n=1,057; mOS = 16.8 months (95% CI: 16.1 – 17.7 months).

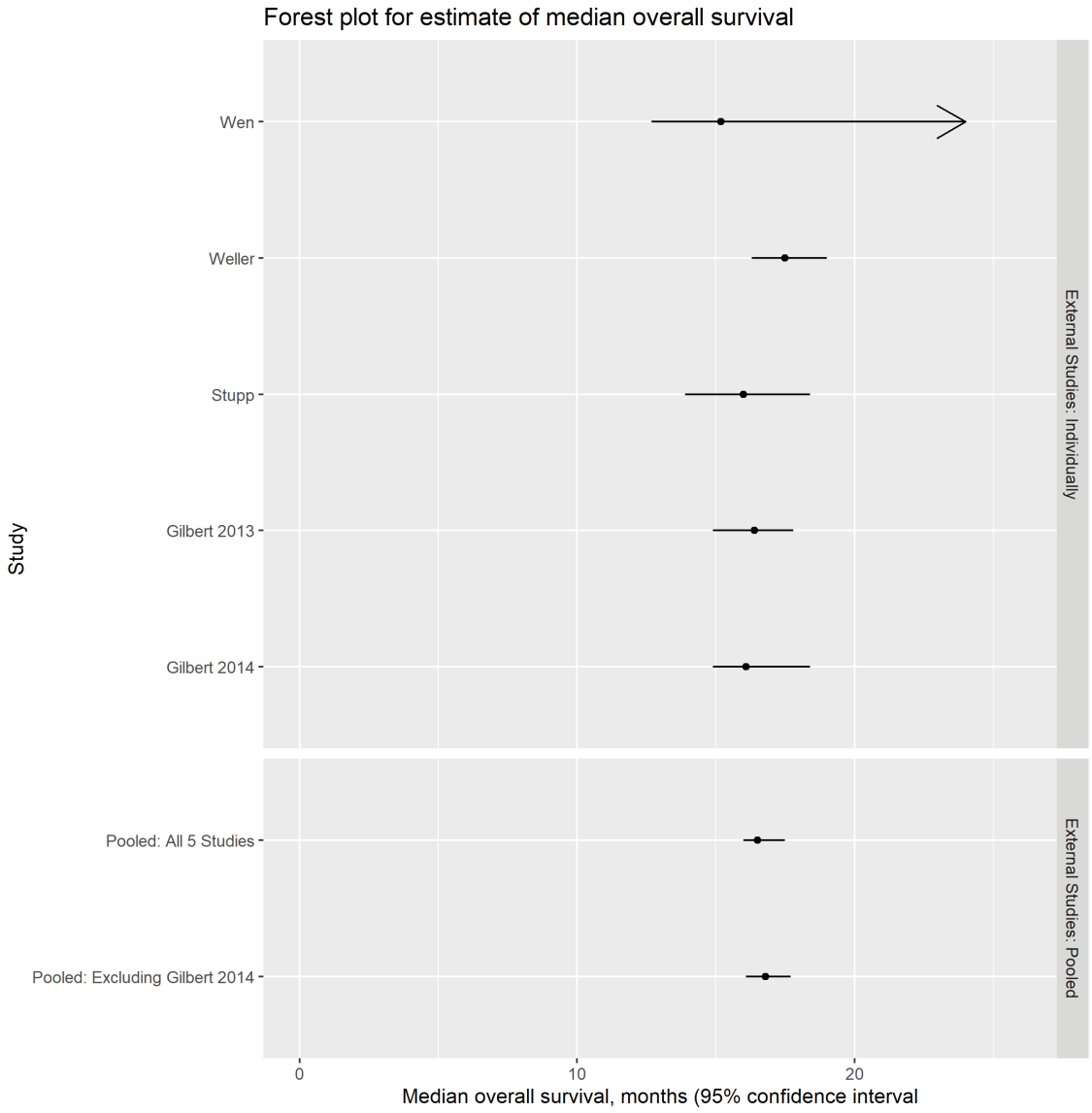
Table 3: Studies selected providing comparable control arms

Lead author	Year	Journal	CONTROL GROUP Treatment	N	Median OS (months)	OS Kaplan-Meier curves available for subgroups
Gilbert	2013	JCO	XRT + temozolomide	411	16.6	MGMT methylated (N = 122), unmethylated (N = 254)
Stupp	2017	JAMA	XRT + temozolomide	229	16.0	Age < 65y (N = 184), Age ≥ 65 y (N = 45), MGMT methylated (N = 77), unmethylated (N = 95)
Weller	2017	Lancet oncology	XRT + temozolomide	374	17.4	Minimal residual disease N = 210), Significant residual disease (N = 163)
Wen	2019	CCR	XRT + temozolomide	43	15.0	None
Gilbert*	2014*	NEJM	XRT + temozolomide	309	16.1	None

*Gilbert 2014 randomized study subjects at an earlier timepoint then the other studies, and all analyses will be conducted both including and excluding this study.

Median overall survival and a 95% confidence interval for the control arm in each of the five studies is shown in Figure 4, demonstrating that the control arms had similar median overall survival.

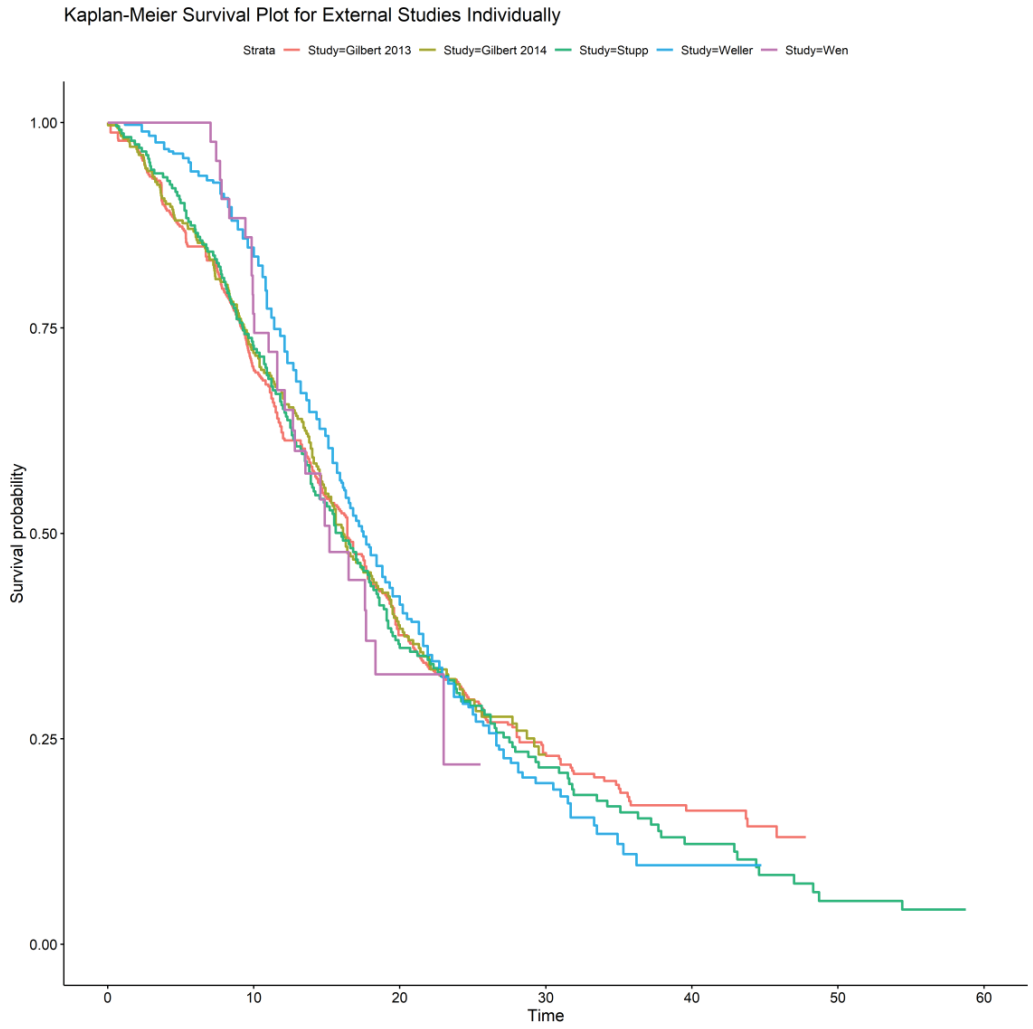
Figure 4: Overall survival comparisons for selected studies: control arms



Study authors of the external studies selected by independent expert review will be contacted to request access to their individual patient data (IPD), for their control groups. Where possible, the original data will be used.

Where the original data are not available, the published Kaplan-Meier survival curves will be digitised and, along with the number at risk at each time (where available), will be used to re-construct the survival and censoring times (IPD) of the control arm subjects in the external studies using the Guyot method [17]. Figure 5 shows the re-constructed Kaplan-Meier survival curves for the control arms for the five example studies, constructed by digitization and overlaid.

Figure 5: Kaplan-Meier overall survival curves for selected studies



8.1.4 Comparison of treatments: if original data are available for external studies

For each study where the original IPD are available, a Cox proportional hazards regression will be conducted comparing the pooled control groups from the external studies with DCVax®-L. Covariates will be included as available. A hazard ratio and 95% confidence interval will be determined.

Kaplan-Meier estimates of the survival functions for the DCVax®-L population and the comparator population will be plotted and estimates of survival (with 95% confidence intervals) at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be calculated. Conditional survival and subgroup comparisons will be estimated similarly.

In addition, if original IPD from the comparator studies are available, a matched case-control comparison based on known prognostic factors may be feasible and may be conducted as a sensitivity analysis.

8.1.5 Comparison of treatments: if only published data are available for external studies

Primary analysis: simple proportional hazards models, external studies pooled

Where the original data are not available, the primary analysis will be a comparison between the reconstructed individual patient survival data reconstructed (by digitizing the published KM curves), for all subjects, pooled across the external studies, with the 232 subjects randomized to DCVax®-L. This analysis will include the published data from all of the studies independently selected to serve as controls for the Trial, regardless of whether they have been included with their IPD in the analysis above. For the MGMT methylated subgroup comparison, the individual patient data will be reconstructed for the external studies where the Kaplan-Meier curves are available for the subgroup (199 subjects in total for the 5 studies identified).

For the other subgroup comparisons, the individual patient data will be reconstructed for the external studies where the Kaplan-Meier curves are available for the subgroup. The following subgroups would be possible for the 5 studies identified to date, with the stated numbers of subjects (available from the external control populations) in each (see Table 3). Other subgroups may also be available if further studies are identified in the independent literature review. The subgroups will be analyzed in the following order:

- MGMT promoter methylated N = 199
- Minimal residual disease N = 210
- Age < 65: N = 184
- MGMT unmethylated: N = 349
- Age >= 65: N = 45
- Significant residual disease: N = 163

Overall survival

- The hazard ratio will be constructed for OS.

Survival conditional on survival to M months

- The hazard ratio will be constructed for CS (conditional on survival to M months).

Overall survival for subgroups

- The hazard ratio will be constructed for OS for the MGMT methylated.
- The hazard ratio will be constructed for OS for other subgroups similarly where possible.

The confidence intervals for the hazard ratios will be constructed in line with the significance levels shown in Figure 3.

Kaplan-Meier estimates of the survival functions for the DCVax®-L population and the pooled comparator population will be plotted and estimates of survival (with 95% confidence intervals) at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be calculated.

Sensitivity analysis 1: Matching-adjusted indirect comparison (MAIC), external studies pooled

A matching-adjusted indirect comparison (MAIC) will be used to compare the treatment groups. The MAIC technique is explained in detail in Appendix D.

Overall survival

The MAIC will be adjusted for the following characteristics.

Table 4: Characteristics to be matched via MAIC: selected studies

Characteristic	*Number of studies*	*Categories*	
MGMT methylation status	5	methylated	unmethylated
Performance status (KPS)	4	< 90%	>= 90%
Surgical status	4	Complete resection / minimal residual disease	Incomplete resection / significant residual disease
Sex	5	M	F
Race	4	White	Non-white
Age	5	Continuous	

The numbers of subjects in each subgroup will be calculated for each study where the information is available. For factors where the information is available for all external studies, the overall proportions across all 1,366 subjects can then be calculated. For factors recorded in only four out of the five studies, the proportion of subjects in those studies will be applied to all the 1,366 subjects for the purposes of matching.

For the pooled published studies, the reconstructed IPD will be compared to the weighted data resulting from matching (see Appendix D) from the DCVax®-L subjects. A Cox proportional hazards model will be used to estimate the treatment effect in the form of a hazard ratio.

Kaplan-Meier estimates of the survival functions for the weighted DCVax®-L population and the comparator population will be plotted and estimates of survival to 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be calculated (with 95% confidence intervals).

Survival conditional on survival to M months

Conditional survival analysis using MAIC weights will not be feasible using published data, but will be conducted if original individual patient data are available.

Overall survival for subgroups

It may not be feasible to analyse survival in subgroups using the MAIC approach if the proportions of subjects with the relevant characteristics are not known for the subgroups unless the original data is available from comparator studies. If such data is available, this analysis will be conducted.

Sensitivity analysis 2: Matching-adjusted indirect comparison, external studies individually and combined

Overall survival

For each published study, the reconstructed IPD will be compared to the correspondingly weighted data from the DCVax®-L subjects. A Cox proportional hazards model will be used to estimate the treatment effect in the form of a hazard ratio.

Kaplan-Meier estimates of the survival functions for the weighted DCVax®-L population and the comparator population will be plotted and estimates of survival to 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be calculated (with 95% confidence intervals).

Survival conditional on survival to M months

It may not be feasible to analyse conditional survival using this approach if the proportions of subjects with the relevant characteristics are not known for the subgroup surviving to at least M months unless the original data from comparator studies is available. If such data is available, this analysis will be conducted.

Overall survival for subgroups

It may not be feasible to analyse survival in subgroups using this approach if the proportions of subjects with the relevant characteristics are not known for the subgroups unless the original data from comparator studies is available. If such data is available, this analysis will be conducted.

Comparison of OS for treatments pooled across external studies

For each endpoint, the hazard ratio (HR) estimates and associated confidence intervals will be combined across the external study comparisons using a random effects meta-analysis (on the log scale) [18]. This combined HR estimate will include an upper confidence limit estimate at the relevant alpha level (see section 8.1.1).

8.1.6 Subgroup analyses for OS and CS

The analyses described for OS and CS will all be repeated for each of the following subgroups, where the data allow.

Table 5: Planned subgroup analyses

Characteristic	***Subgroups***
• Methylation status (MGMT):	• Methylated, unmethylated
• Extent of resection:	• Complete, partial
	• Significant, minimal residual
• Age categories:	• 18-40, 41-50, 51-60, 61-64, ≥65
• Sex:	• Male, female
• KPS:	• 70 – 80, > 80 - 90, > 90 – 100
• Baseline lymphocyte count (/µL):	• ≤ median, > median
	• ≤ 1,000, > 1,000
	• ≤ 1,250, > 1,250
• RPA[10] classification:	• Class III, Class IV
• Race:	• Caucasian, non-Caucasian
• Residual tumor size:	• Measurement; also quartiles
• PD-L1 expression in tumor tissue:	• High, Low
• PD-L1 status of circulating monocytes:	• > 80% positive cells, ≤ 80%
	• > 50% positive cells, ≤ 50%
	• >10% positive cells, ≤ 10%
• Pre-existing CD8 T-cell density:	• ≤ median, > median
• Immunological responders to DCVax®-L:	• Yes, No
• Histology - GBM subtype:	• Proneural, Neural, Classical, Mesenchymal
• Immunoscore:	• 0 through 5
• Biomarker status:	• EGFR and PTEN genes, IDH1 WT, 1p19q intact
• Rapid progressors (subjects with PFS ≤ 2m):	• Yes, No
• Early progressors: (subjects with PFS ≤ 4m):	• Yes, No

8.2 Analysis for OS in recurrent GBM: comparison with external study control groups

This endpoint, will apply to those subjects who were originally assigned to the placebo arm and who received standard of care + placebo until disease progression, and who then crossed over to receive DCVax®-L post-progression. The survival of these subjects will be analyzed via comparison to external studies in recurrent GBM.

Secondary analyses will evaluate the same endpoint of OS post progression for the following populations:

[10] For this study population: Class III: Age < 50 and KPS ≥ 90. Class IV: Age < 50 and KPS < 90, or Age ≥ 50.

- Patients who were originally assigned to DCVax®-L, and who received DCVax®-L under the crossover option following progression
- All patients, irrespective of original treatment assignment, who received DCVax®-L under the crossover option following progression

A systematic literature review for recurrent GBM studies has been conducted by independent experts to identify appropriate studies in recurrent GBM from which survival data for control groups could be obtained, in the same manner as the independent expert selection of the appropriate external studies for newly diagnosed GBM. The control patients from ten studies shown in Table 6 [5, 19-27], which were conducted in similar populations as in the current Phase III study, in trials which each had a control arm will be included. The control patients were treated with physician's choice of therapy or best available standard treatment, which could include standard treatments like lomustine or bevacizumab.

Table 6: Studies selected providing comparable control arms: recurrent GBM

Lead author	Year	Journal	CONTROL GROUP			OS Kaplan-Meier curves
			Treatment arm	N	Median OS (months)	available for subgroups of interest
Brandes	2018	The Oncologist	Lomustine plus placebo	62	5.5	None
Wick	2017	NEJM	Lomustine	149	8.6	None
Wick	2010	JCO	Lomustine	92	7.1	None
Brandes	2016	Neuro-Oncology	Lomustine plus placebo	40	7.5	None
Lombardi	2019	Lancet Oncology	Lomustine	60	5.6	None
Taal	2014	Lancet Oncology	Best supportive care	30	8.0	None
Narita	2017	Neuro-Oncology	Lomustine	46	8.0	None
Cloughesy	2017	JCO	Bevacizumab plus placebo	65	12.6	MGMT methylated (N = 26), unmethylated (N = 25)
Galanis	2019	Cancer	Bevacizumab plus placebo	38	7.7	None
Lee	2020	Cancer	Bevacizumab plus placebo	58	11.5	None

Assuming original data are not available, the published Kaplan-Meier survival curves will be digitised and, along with the number at risk at each time (where available), will be used to re-construct the survival and censoring times (IPD) of the control arm subjects in the external studies using the Guyot method [17].

8.2.1 Primary analysis: simple proportional hazards model

The primary analysis will be a comparison between the reconstructed individual patient data for all subjects, pooled across the external studies, with the subjects who crossed over from the placebo arm and were treated with DCVax®-L post-progression. Cox's proportional hazards model will be used.

Median survival and a 95% confidence interval will be reported.

The hazard ratio (HR) and a 95% confidence interval will be reported, as well as the associated 2-sided p value. Estimates of survival probability at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be calculated (with 95% confidence intervals).

Kaplan-Meier estimates of the survival functions for the DCVax®-L population and the comparator population will be plotted.

8.2.2 Subgroup analyses

The same analysis will be repeated within the MGMT methylated and MGMT unmethylated subgroups. The individual patient data will be reconstructed from digitized KM plots for the single external study where the Kaplan-Meier curves are available for these subgroups.

8.2.3 Sensitivity analysis: Matching-adjusted indirect comparison, external studies in turn

For each external study separately, a matching-adjusted indirect comparison (MAIC) will be used to compare the control group in that study with the treatment group in the DCVax®-L trial. The MAIC technique is explained in detail in Appendix D.

The MAICs will be adjusted for the following characteristics.

Table 7: Characteristics to be matched via MAIC: selected studies, recurrent GBM

Study	MGMT	KPS	Age	Sex	Race
Brandes 2018	✓	✓	✓	✓	
Wick 2017	✓		✓	✓	
Wick 2010		✓	✓	✓	
Brandes 2016			✓	✓	✓
Lombardi 2019	✓		✓	✓	
Taal 2014	✓		✓	✓	
Narita 2019		✓	✓	✓	
Cloughesy 2017	✓	✓	✓	✓	✓

Study	MGMT	KPS	Age	Sex	Race
Galanis 2019			✓	✓	
Lee 2020		✓	✓	✓	✓

The hazard ratio and a 95% confidence interval as well as a 2-sided p value will be reported. Estimates of survival probability at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be calculated (with 95% confidence intervals).

8.2.4 Secondary analyses

Secondary analyses will repeat the analyses above for the following populations:

- Patients who were originally assigned to DCVax®-L, and who received DCVax®-L under the crossover option following progression. This comparison investigates whether 'priming' with DCVax®-L may result in a benefit;
- All patients, irrespective of original treatment assignment, who received DCVax®-L under the crossover option following progression. This comparison investigates the impact of DCVax®-L on survival for patients who experience disease recurrence, irrespective of their treatment prior to recurrence.

8.3 Statistical methods for the analysis of the secondary endpoints: comparisons internal to the DCVax®-L study

8.3.1 Type I error

The secondary endpoints will be tested in the order shown in Table 2, Section 3, using a gatekeeping approach whereby an endpoint is tested for significance if its predecessor is significant at 2.409%.

8.3.2 Analysis for OS, PFS

The intent of the original protocol was that the Cox proportional hazards model will be used for the primary analysis of OS. However the OS endpoint analysis may be confounded by non-proportional hazards due to the effects of the crossover option that was built into the protocol from the outset. Under this crossover option, all subjects from both arms of the Trial were allowed to opt to receive the active treatment DCVax®-L at the time of disease progression (measured by MRI), while remaining blinded to their initial treatment assignment. If subjects originally assigned to placebo receive treatment benefit in terms of extended survival as a result of this crossover option, then we can expect the survival curves to converge. To address possible non-proportionality while controlling type I error, a testing procedure based on a weighted log-rank statistic that was developed by Karrison will be used [28].

The intent of the original protocol was that the Cox proportional hazards model will be used for the primary analysis of PFS. When the protocol was developed in 2006 the phenomenon of pseudo-progression was largely unknown. Since then, pseudo-progression has become well recognised as a

major issue. It is now expected that, because early events specifically may not represent true disease progression, differentially in the two randomized groups, the proportional hazards assumption may not hold; the hazard ratio is expected to decrease with time as the effect of PsPD decreases.

For OS and PFS, Karrison's approach to the weighted log rank test will be used [28], based on the ITT population. A one-sided p value will be presented.

Along with the p value for the test, the hazard ratio, with a 95% confidence interval, will be presented. Estimates of 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 month OS and PFS will be provided, with 95% confidence intervals, for both randomized treatment groups.

8.3.3 Analysis for confirmed PFS

For confirmed PFS, the Cox proportional hazards model will be used.

8.3.4 Exploratory analyses

The following alternative approaches to the statistical analysis of OS, PFS and cPFS will be conducted as exploratory analyses.

1. OS, PFS and cPFS: Cox model (ITT)

A Cox proportional hazards regression model [29] based on the ITT population will be used. The following baseline covariates will be assessed (one at a time) for their additional contribution to the statistical model, and each covariate showing a significant ($P < 0.05$) contribution will be included in the final model, for each endpoint separately. Subjects with missing data in the continuous variables (age, KPS) will be excluded from the respective analysis. Hazard ratios, estimates of survival to 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months and 95% confidence intervals will be provided.

- Sex: Male / female
- Age at randomization: years
- MGMT status at randomization: Yes, No, unknown
- Karnofsky Performance Status at randomization: score
- Extent of resection: Complete, partial (or incomplete), unknown
- Absolute lymphocyte count at randomization: ≤ 1,000 /µL, > 1,000/µL, unknown

2. OS, PFS and cPFS: Segmented (piecewise) Cox model (ITT)

The categorical, time-dependent, covariate PH model [29] tests whether the effect (coefficient) of a covariate changes with time (i.e. non-constant hazard ratio) over time segments of the study. This method has appeal because it not only detects non-proportionality, but allows it to be modelled validly. If the non-proportionality is linear, dichotomizing time could be sufficient. Alternatively, time could be categorized into four or five groups [30]. Within these groups, the assumption that the covariate effect is linear is more reasonable. There should be relatively equal numbers of events and censored observations across the time intervals to endure that the standard errors of the parameter estimates are relatively similar. Interactions are tested using the same likelihood test. The choice of time segments will be data driven; therefore, this analysis is not fully specified in this document.

3. OS, PFS and cPFS: Cox model (PP)

The analyses described for the ITT population will be repeated in the PP population.

4. OS, PFS and cPFS: Biomarker subgroups

The analyses described for the ITT population will be repeated in the ITT population excluding subjects with IDH-1 mutation and/or with chromosome 1p19q co-deletions.

8.3.5 Further subgroup analyses for OS and PFS

The analyses described for the ITT population will all be repeated for each of the following subgroups (as in Table 5 above).

Table 8: Planned subgroup analyses

Characteristic	***Subgroups***
• Methylation status (MGMT):	• Methylated, unmethylated
• Extent of resection:	• Complete, partial • Significant, minimal residual
• Age categories:	• 18-40, 41-50, 51-60, 61-64, ≥65
• Sex:	• Male, female
• KPS:	• 70 – 80, > 80 - 90, > 90 – 100
• Baseline lymphocyte count (/µL):	• ≤ median, > median • ≤ 1,000, > 1,000 • ≤ 1,250, > 1,250
• RPA classification:	• Category III, category IV
• Race:	• Caucasian, non-Caucasian
• Residual tumor size at baseline:	• Based on quartiles
• PD-L1 expression in tumor tissue:	• High, Low
• PD-L1 status of circulating monocytes:	• > 80% positive cells, ≤ 80% • > 50% positive cells, ≤ 50% • >10% positive cells, ≤ 10%
• Pre-existing CD8 T-cell density:	• ≤ median, > median
• Immunological responders to DCVax®-L:	• Yes, No
• Histology - GBM subtype:	• Proneural, Neural, Classical, Mesenchymal
• Immunoscore:	• 0 through 5
• Biomarker status:	• EGFR and PTEN genes, IDH1 WT, 1p19q intact
• Rapid progressors (subjects with PFS ≤ 2m):	• Yes, No
• Early progressors: (subjects with PFS ≤ 4m):	• Yes, No

The hazard ratio for the treatments, and a 95% confidence interval for the HR, will be estimated for each subgroup.

8.4 Statistical methods for the analysis of the exploratory efficacy endpoints: comparisons internal to the DCVax®-L study

8.4.1 Immunostimulatory response

A subject will be considered a responder if one of the following conditions holds:

- T cell proliferative response to DCVax®-L shows a stimulation index of 2 or greater;
- A greater than 3-fold increase in CD8+ cells staining with tumor antigen tetramers.
- An ELISPOT response exceeding background signal by at least 2 standard deviations. The background signal will be based on the level of response in patients randomized to placebo

Immunostimulatory response will be analyzed as a binary outcome. Logistic regression will be used, with the following covariates:

- Sex: Male / female
- Age at randomization: years
- MGMT status at randomization: Yes, No, unknown
- Karnofsky Performance Status at randomization: score
- Extent of resection: Complete / partial (or incomplete)
- Absolute lymphocyte count at randomization: ≤ 1,000 /µL, > 1,000/µL, unknown

8.4.2 Physical functioning

Physical functioning will be measured by the Karnofsky performance status (KPS). Both the score and the change from baseline will be summarized, and the change from baseline will be compared between the treatment groups and the controls groups using the Wilcoxon test stratified by MGMT methylation status. This analysis will be conducted for each visit separately.

The time from date of surgical resection to a 10-point decline in KPS will calculated. This endpoint will be analyzed using the Karrison approach as for the analysis of the secondary endpoints within study PFS and OS.

8.4.3 Time to progression (TTP)

Time to progression (TTP) is defined as the time from randomization to disease progression (per modified Macdonald criteria determined by independent ICON Medical Imaging review). Progression is censored when a uuPD occurs. For patients who die before experiencing progression or uuPD, progression is censored at death. Within-Study controls are used for this endpoint.

TTP will be analyzed using a cause-specific Cox proportional hazards regression model [31].

8.4.4 Tumor response

Tumor response will be defined in three ways:

- Complete response
- Complete or partial response
- Complete or partial response or stable disease.

Each will be analyzed as a binary outcome. Logistic regression will be used, with covariates as defined for the primary analysis of the primary endpoints.

8.4.5 Ultimately unconfirmed progression

A KM plot of the percentage of subjects who had a progression event during the trial and who are free of uuPD events (as defined in Section 3.2.5) versus time by treatment arm is intended to aid in the interpretation of influence of vaccine-induced, pseudo-progression, if any, on the analysis of the primary and secondary endpoints. One example is that an increase incidence over time in the intervention group relative to the control group in uuPD could possibly be an indication of the presence of vaccine-induced, pseudo-progression in the analysis of OS, cPFS and PFS.

Overall survival will be compared between patients who had a progression event during the trial and then experience an uuPD and those that experience a cPD, regardless of treatment group.

Section 9: Safety

9.1 Adverse events

An overall summary will present the number and percentage of subjects by treatment group with:

- Any TEAE
- Any serious TEAE
- Any TEAE considered as related to study drug, evaluated by the investigator as Definitely Related, Possibly Related or Probably Related or not reported
- Any TEAE considered as related to leukapheresis, evaluated by the investigator as Definitely related, Possibly Related or Probably Related or not reported
- Maximum CTCAE of grades 1 to 5; i.e. a subject with TEAEs at different CTCAE grades will be summarized at the most severe grade
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to death

The summary will also include the total number of TEAEs reported in each treatment group.

The number and percentage of subjects with TEAEs will be presented by SOC, PT and treatment group. Subjects with multiple TEAEs within a SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination. Similar summaries will be presented for related TEAEs, serious TEAEs, related serious TEAEs, and TEAEs leading to discontinuation of study drug. TEAEs with CTC Grade 3 or above, and related TEAEs with CTC Grade 3 or above, will be summarized.

Summaries of TEAEs by maximum CTCAE grade will also be presented.

All TEAEs will be listed by subject and start date.

Injection site TEAEs will be listed separately.

9.2 Physical examination

Physical examinations were conducted at each visit. The following systems are also assessed; an 'Other' category was also included:

- General appearance
- Head, eyes, ears, nose, throat
- Skin/dermatologic
- Lymph nodes
- Chest / lungs
- Heart /cardiovascular
- Abdomen
- Extremities

Each was assessed on a 3-point scale:

- Normal or return to normal
- Abnormal not clinically significant
- Abnormal clinically significant

Results and changes from baseline will be summarized per visit, for each treatment group separately.

9.3 Neurological examination

Neurological examinations were conducted at each visit. The following systems were assessed; an 'Other' category was also included:

- Mental status
- Cranial nerves
- Motor
- Reflexes
- Sensory
- Coordination / gait

Each was assessed on a 3-point scale:

- Normal
- Abnormal due to GBM
- Abnormal due to other causes

Results and changes from baseline will be summarized per visit, for each treatment group separately.

9.4 Laboratory tests

Laboratory test results will be summarized for each treatment group separately. Shift tables will be prepared.

9.5 Vital signs

The following will be presented in tables summarizing by-treatment descriptive statistics for the observed and change from baseline values at each visit:

- Pre-injection heart rate
- Systolic blood pressure (BP)
- Diastolic BP
- Respiration

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APPENDIX A: External controls for newly diagnosed GBM

Report 1 from YHEC, attached to PDF

APPENDIX B: External controls for recurrent GBM

Report 2 from YHEC, attached to PDF

APPENDIX C: Progression-free survival

Situation	Date of Progression or Censoring	Outcome
Progression documented between scheduled visits	Actual date of documented progression	Progression
No progression	Date of last radiology assessment demonstrating no progression	Censored
Treatment discontinuation for undocumented progression	Date of last radiology assessment demonstrating no progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiology assessment demonstrating no progression	Censored
New anticancer treatment started	Date of last radiology assessment demonstrating no progression	Censored
Progression after more than one missed visit	Date of last radiology assessment demonstrating no progression	Censored
Death before first PD assessment	Date of death	Progression
Death between adequate assessment visits	Date of death	Progression
Death after one or two missed visits (≤ 4 months from last MRI)	Date of death	Progression
Death after more than two missed visits (> 4 months from last MRI)	Date of last radiology assessment demonstrating no progression	Censored
No MRI post baseline and no death within 4 months of baseline and withdrawn from study	Date of withdrawal	Censored

In practice, this is executed as follows:

Take the minimum of the following dates

- Confirmed Progression
- Death
- Withdrawal due to reason "OTHER", "DISEASE PROGRESSION" or "PATIENT ENROLLED IN A TRIAL OF ANOTHER INVESTIGATIONAL AGENT FOR THE TREATMENT OF GBM"

Depending on which of these dates is the minimum decides how PFS is calculated. It is possible that all three of these dates are missing for a patient and therefore they have no minimum date. When two different dates are both the minimum date and it needs to be decided which set of rules to follow then the rules are picked using priority Confirmed Progression > Death > Withdrawal.

e.g. a patient has a confirmed progression and a withdrawal on the same day, both of which occur before death. Use the Confirmed progression rule to derive PFS because Confirmed Progression > Withdrawal.

Minimum Date	**Rule to determine PFS date and censoring**
Confirmed Progression	• If their last MRI prior to progression was within 4.5 months of their progression, then use confirmed progression date, uncensored • Otherwise use previous MRI, censored
Death	• If subject died within 2 months of randomization, use date of death, uncensored • If the subject died within 4.5 months of an MRI scan use date of death, uncensored • Otherwise use previous MRI, censored
Withdrawal due to one of the specified reasons	• Use last MRI prior to withdrawal, censored
No minimum date	• Use the last MRI, censored

In the above table there are various conditions which require to use the last MRI as the PFS date. However there are cases when the subject either does not have MRI data or the last MRI was pre baseline. In these cases use the date of study completion, censored.

APPENDIX D: Matching-Adjusted Indirect Comparison

Matching-adjusted indirect comparison (MAIC) is a technique that is commonly used to help inform cost-effectiveness modelling: an area where treatment effect estimates are frequently required for treatments not compared within the same trial or in trials with a common comparator treatment [32]. MAIC aims to adjust for differences in subject characteristics (both prognostic factors and treatment effect modifiers) between trials, in order to compensate for a lack of randomization, or imbalances between studies. Note that this method relies on the unverifiable assumption that outcomes can be fully predicted from the treatment and that all important prognostic factors and effect modifiers are included in the model [32].

Subject characteristics are identified that are reported in the current phase III study (Study 020221) and in the published data for the control arm. Subjects in the DCVax®-L arm of Study 020221 are then given weights such that overall the weighted averages of their characteristics match those of the control arm of the published study. Characteristics that can be included in some or all of these analyses, depending on what was reported for the control arm in question, are:

- MGMT methylation status
- Performance status
- Surgical status
- Age
- Sex
- Race

More specifically, it is assumed that we have a treatment k_1 that has been studied in population s_1 for which individual patient data (IPD) of covariates $X_{s1} = \{x_i s_1\}$ are available, and a second population s_2 where the treatment has not been studied, and where only the marginal means of the covariate data $\bar{X}_{s_2}$ are available. The principle of the method is to translate the observed study results $Y_{k_1 s_1 = \{y_i\}}$ in study population s_1 to expected mean study results $\hat{Y}_{k_1 s_2}$ by weighting the population in study s_1 to make it more similar to population s_2. This is done using the following steps:

1) Re-centre the covariate vectors by subtracting $\bar{X}_{s_2}$, thereby generating two new vectors, $X'_{s1} = X_{s1} - \bar{X}_{s_2}$ and $\bar{X}'_{s_2} = 0$
2) Find the values $\hat{\alpha}$ that minimize $\sum_{i=1}^{N_{s_1}} \exp\left(\alpha^T x'_{is_1}\right)$.
3) Apply survival analysis to the reweighted data.

Standard errors will be estimated using a robust sandwich estimator [33].

A MAIC will be performed for all the published studies pooled together, and also separately for each published study.

As a part of evaluating the performance of the weighting, the adjusted sample size will be calculated and reported for each MAIC. This can be calculated as

$$Adjusted\ sample\ size = \frac{(\sum weights)^2}{\sum weights^2}$$

A Phase III Clinical Trial Evaluating DCVax®-L, Autologous Dendritic Cells Pulsed with Tumor Lysate Antigen for the Treatment of Glioblastoma Multiforme

Version 7.0
Amendment 5 September 23, 2020

Study Agent: DCVax®-L (Autologous Dendritic cells and GBM tumor lysate)
Protocol Number: 020221
IND Number: 10206

Sponsor: **Northwest Biotherapeutics, Inc.**
Address: 4800 Montgomery Lane, Suite 800, Bethesda, MD 20814
Phone: 240 497 9024
Fax: 240 627 4121

EudraCT Number: 2011-001977-13

This protocol has been approved by Northwest Biotherapeutics, Inc. The following signature documents this approval.

_____
Marnix Bosch, MBA, PhD (signature)
Chief Technical Officer

Principal Investigator Agreement:

I the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice and the ethical principles set forth in the Declaration of Helsinki, and to abide by all applicable local and national regulatory requirements.

Signature: _____ Date: _____

Print name: _____ Site Number: _____

Protocol Synopsis

Protocol Title: A Phase III clinical trial evaluating DCVax®-L, autologous dendritic cells (DC) pulsed with tumor lysate antigen for the treatment of glioblastoma multiforme (GBM)

Protocol No.: 020221, v7.0

Study Agent: DCVax®-L (autologous DC loaded with autologous tumor lysate).

Indication: Treatment of patients with newly diagnosed GBM.

Objectives:
Primary: The primary objective of this study is to compare overall survival (OS) between patients randomized to DCVax-L and control patients from comparable, contemporaneous trials who received standard of care therapy only, in patients with newly diagnosed glioblastoma. This endpoint will be assessed using 3 different analyses.

Secondary: The first secondary objective is to compare overall survival (OS) between patients randomized to placebo who received DCVax-L treatment following disease recurrence and control patients from comparable, contemporaneous clinical trials, in patients with recurrent GBM.

Study Design:
The study is designed as a randomized, placebo-controlled, double blinded, multi-center, multi-national Phase III clinical trial.

To achieve its primary goals, the trial will randomize approximately 348 patients with newly diagnosed GBM with no evidence of progression at baseline, of which approximately 232 patients will be randomized into the treatment cohort and will receive DCVax-L as adjuvant therapy to standard treatment and approximately 116 patients will be randomized into the placebo cohort and will receive standard treatment supplemented with autologous mononuclear cells (MNC; placebo).

Patients must have a minimum of 5 doses of DCVax-L available to be eligible for randomization. Randomized patients will receive up to 10 immunizations with DCVax-L or placebo over a period of up to 3 years. Some patients in the DCVax-L cohort may not receive 10 immunizations due to insufficient material; in these cases immunizations will be replaced with placebo while maintaining the blind. Patients in either cohort who progress during the study will be offered a crossover (open-label) option with no unblinding to receive a series of up to 10 immunizations with DCVax-L (depending on DCVax-L availability).

Safety of DCVax-L will be assessed by comparing the frequency and intensity of adverse events, physical and neurological examination, and clinical laboratory testing results during the study period, between DCVax-L treated patients and controls.

Population:
Patients 18 to 70 years old with newly diagnosed GBM (Grade 4 astrocytoma), who will undergo surgery, are eligible to enter into screening. Patients in screening who have received external beam radiation therapy with concurrent temozolomide chemotherapy according to the Stupp protocol guidelines (Stupp et al., N Engl J Med 352: 987-96, 2005), without evidence of disease progression following radiation therapy, are eligible to be randomized into the study. All patients must have a Karnofsky Performance Score (KPS) of ≥70, ≥8 week life expectancy, no other prior malignancy within the last 5 years, and no active infections. See section 7 for full eligibility criteria.

Treatment Schedule:
Two intradermal (i.d.) injections of DCVax-L (active) or autologous MNC (placebo) per treatment; each injection consisting of 1.25 million DC in approximately 0.15 mL, in the upper arm. Injection volume is patient specific and the Certificate of Analysis (C of A) should be referenced. Treatments will be given at days 0, 10, 20, and at months 2, 4, 8, 12, 18, 24 and 30. All Crossover patients will receive the active immunization injections on this schedule, study drug supply availability permitting.

Efficacy Assessments:
Disease progression is assessed every 2 months by central review of brain MRI scans, according to the imaging parameters in the imaging manual. KPS is assessed every 2 months during clinic visits. Immune monitoring labs are drawn at regular intervals throughout the treatment period.

Primary Endpoint and Secondary Endpoint, Hypotheses, and Analytic Method
Primary: The primary objective of this study is to compare overall survival (OS) between patients randomized to DCVax-L and control patients from comparable, contemporaneous trials who received standard of care therapy only, in patients with newly diagnosed glioblastoma.

Hypothesis: Overall survival, measured from time of randomization, will be longer for patients in the DCVax-L cohort compared to patients who received standard of care in other, comparable, contemporaneous trials.

Analytic Method #1: Proportional hazards (Cox) regression.

Analytic Method #2: Conditional Survival analysis

Analytic Method #3: Overall Survival in specific subgroups

Secondary: The first secondary objective is to compare overall survival (OS) between patients randomized to placebo who received DCVax-L treatment following disease recurrence, and control patients from comparable, contemporaneous clinical trials, in patients with recurrent GBM.

Hypothesis: Overall survival, measured from time of disease progression, will be longer for patients in the placebo cohort who received treatment with DCVax-L upon disease progression, when compared to control patients from other comparable contemporaneous clinical trials who received best available care.

Analytic Method: Cox regression.

Secondary: The second secondary objective, confirmed progression-free survival (cPFS), is to compare confirmed disease progression (cPD) between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

Secondary: The third secondary objective, PFS, is to compare progression-free survival between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

Secondary: The fourth secondary objective, OS, is to compare overall survival between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

Secondary: The fifth secondary objective is to compare tumor response between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

Other Endpoints

- To compare the following between subjects in the DCVax®-L arm and subjects in the placebo arm within the Trial:
- Immune profiles in the peripheral blood that may be predictive of response/non-response to immunotherapies
- Decline in physical functioning, measured by Karnofsky Performance Status (KPS) evaluation
- Time to progression of disease (TTP)
- Survival at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months
- Times to PFS, OS and TTP, measured from initial surgery.

To evaluate further the safety profile of DCVax®-L.

Northwest Biotherapeutics, Inc.

DCVax®-L

Protocol 020221, Version 6.2

A Phase III Clinical Trial Evaluating DCVax®-L, Autologous Dendritic Cells Pulsed with Tumor Lysate Antigen for the Treatment of Glioblastoma Multiforme

TABLE OF CONTENTS

LIST OF APPENDICES

1. GENERAL INFORMATION

1.1. PROTOCOL TITLE

A Phase III Clinical Trial Evaluating DCVax®-L, Autologous Dendritic Cells Pulsed with Tumor Lysate Antigen for the Treatment of Glioblastoma Multiforme

1.2. SPONSOR INFORMATION

Northwest Biotherapeutics, Inc.
4800 Montgomery Lane, Suite 800
Bethesda, MD 20814

1.3. PERSONS AUTHORIZED TO SIGN PROTOCOL AMENDMENTS

Alton Boynton, Ph.D., Chief Scientific Officer, Northwest Biotherapeutics, Inc. (NWBT)
Marnix Bosch, M.B.A., Ph.D., Chief Technical Officer, NWBT

1.4. INVESTIGATOR INFORMATION

A list of Investigators and sites participating in this study is on file at NWBT.

1.5. CONTRACTORS AND CONSULTANTS FOR THE STUDY

See Appendix G.

2. INTRODUCTION TO THE PROTOCOL

2.1. INTRODUCTION

DCVax-L was used in a Phase I/II clinical trial to immunize patients with GBM (Grade 4 astrocytoma), following primary therapy that consisted of surgery, followed by conventional external beam radiation and temozolomide chemotherapy during radiation and for six cycles after radiation. No serious adverse events (SAE) attributable to the study drug were observed. Based on promising data in patients with GBM indicating slowing of disease progression and increased survival, the following Phase III study, which is designed as a pivotal study, will be conducted in patients presenting with newly diagnosed GBM.

2.2. PHASE I/II CLINICAL TRIALS

The results of the Phase I/II trials to test the safety and efficacy of DCVax-L are briefly summarized below, and are more fully described in the accompanying Investigator's Brochure (IB). There is an abundance of cancer literature supporting the safety and potential efficacy of using autologous DC pulsed with autologous tumor lysate antigen, in which 43 trials involving 903 patients are described, with no evidence of serious toxicities or autoimmunity (see IB for a complete listing of references).

The Phase III protocol is predicated on two Phase I/II trials (BB-IND #8434 and #11053) carried out by Dr. Linda Liau and Dr. Robert Prins at the University of California, Los Angeles (UCLA).
Twenty (20) patients with newly diagnosed GBM have been enrolled in 2 Phase I/II trials (data as of June 2011). Patients have been followed for up to 10 years. Sixteen patients have surpassed the historical median time to progression (TTP) of 8.9 months, without evidence of disease progression. Overall, 16 patients have progressed; the four patients with no progression of disease have follow-up times ranging from 43 to 122 months from surgery; these are also the only 4 patients who

are still alive. Median progression free survival in these 20 patients is 26.4 months (when McDonald's criteria are used), and median survival time is 35 months. Historically, at the same institution (UCLA), patients similar to those enrolled in the trial (R.P.A. classes III and IV) have median times to disease progression of 8.9 months (± 7.3 months), and median survival times of 15 months (± 13.9 months).
In a multicenter trial, 287 patients treated post surgery with radiotherapy plus concomitant temozolomide achieved median progression free survival (PFS) of 6.9 months from surgery (95% confidence interval, 5.8 to 8.2) and median survival of 14.6 months from surgery (95% confidence interval, 13.3 to 16.8; Stupp, 2005). In the Phase II trial, PFS and survival times will be calculated from time of randomization, which is expected to occur approximately three months after initial surgery.

Adverse events: To date, there have been no serious adverse events related to the study drug. Non-serious adverse events including mild symptoms of nausea/vomiting, headache, fatigue, diarrhea, low-grade fever and loss of appetite were the most common symptoms that could possibly or likely be associated with the treatment. Lymph node swelling, myalgia, arthralgia, back/neck pain, depression, dehydration, hiccoughs, dizziness, cough, somnolence, dyspnea, allergic rhinitis, and pain/itching at injection site were other less common symptoms reported. Most AEs and all SAEs were deemed related to disease progression.

3. OVERVIEW OF DCVAX-L PHASE III CLINICAL TRIAL

This protocol describes a randomized, placebo-controlled, double blinded, multi-center, multi-national Phase III clinical trial for DCVax-L in patients with newly diagnosed GBM (DCVax-L, when used for primary brain cancer, is sometimes referred to as DCVax-Brain). The primary endpoint for the study is Overall Survival compared to external controls. The study is powered to detect meaningful clinical benefit for this . Secondary endpoints include survival in patients with disease recurrence compared to external controls, confirmed progression-free survival, and tumor response, as well as the original trial endpoints PFS and OS. Other (tertiary) endpoints include time to progression (TTP), decline in Karnofsky Performance Status (KPS), landmark analyses of survival, and immune responses to DCVax-L.

The underlying hypothesis is that DCVax-L, i.e. DC generated from the peripheral blood of a patient with GBM and loaded (combined) with tumor lysate antigen, will safely (1) delay time to disease progression, (2) increase survival and (3) induce anti-tumor immunity when administered as a series of intradermal (i.d.) injections in newly diagnosed patients. DCVax-L is intended as adjuvant therapy to standard primary treatments, which include surgical resection, external beam radiation therapy with concurrent temozolomide chemotherapy, followed by additional cycles of temozolomide chemotherapy essentially following the protocol guidelines according to Stupp et al. (N Engl J Med 352: 987-96, 2005; "The Stupp Protocol"). Administration of adjuvant temozolomide is minimally modified from the guidelines to allow for vaccine dose window adherence.

3.1. OBJECTIVES

3.1.1. Primary objective

The primary objective of this study is to compare overall survival (OS) between patients randomized to DCVax-L and control patients from comparable, contemporaneous trials who received standard of care therapy only, in patients with newly diagnosed glioblastoma.

Hypothesis: Overall survival, measured from time of randomization, will be longer for patients in the DCVax-L cohort compared to patients who received standard of care in other, comparable, contemporaneous clinical trials.

Analytic Method #1: Proportional hazards (Cox) regression.

Analytic Method #2: Conditional survival analysis

Analytic Method #3: Overall survival in specific subgroups

3.1.2. Secondary objective

The first secondary objective is to compare overall survival (OS) between patients randomized to placebo who received DCVax-L treatment following disease recurrence, and control patients from comparable, contemporaneous clinical trials, in patients with recurrent GBM.

The second secondary objective, confirmed progression-free survival (cPFS), is to compare confirmed disease progression (cPD) between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

The third secondary objective, PFS, is to compare progression-free survival between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

The fourth secondary objective, OS, is to compare overall survival between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

The fifth secondary objective tumor response, is to compare tumor response rates between subjects randomized to DCVax®-L and those randomized to Placebo within Study 020221.

3.1.3. Tertiary objectives

- To compare immune responses between patients in the treatment cohort and patients in the placebo cohort for all randomized patients (i.e., patients randomized at baseline with no evidence of disease progression); The percentage of patients mounting a T cell response to tumor antigens is expected to be higher in patients immunized with DCVax-L when compared to patients immunized with the placebo;
- To compare decline in physical functioning, measured by KPS evaluation, between patients in the treatment cohort and patients in the placebo cohort for all randomized patients (i.e., patients randomized at baseline with no evidence of disease progression). Patients in the treatment cohort are expected to experience a slower rate of decline in physical functioning than patients in the placebo cohort.;

- To compare time to progression of disease (TTP; includes as events all radiographic evidence of disease progression; all deaths are censored) between patients in the treatment cohort and patients in the placebo cohort for all randomized patients (i.e., patients randomized at baseline with no evidence of disease progression). TTP is expected to be longer for patients in the treatment cohort than for patients in the placebo cohort.;

- To compare survival at 6, 12, 18, 24, 36 and 48 months between patients in the treatment cohort and patients in the placebo cohort for all randomized patients (i.e., patients randomized at baseline with no evidence of disease progression). The percentage of patients surviving at these time points is expected to be greater in the treatment cohort than in the placebo cohort.

3.1.4. Safety objective

To evaluate further the safety of DCVax-L.

3.2. STUDY POPULATION

Patients with newly diagnosed GBM are eligible for this protocol. Diagnosis of GBM will be confirmed through independent central pathology review. Patients must have a surgically accessible, unilateral tumor for which surgical resection, with intent to perform a gross total **or** near gross total resection, is indicated.

3.3. STUDY DESIGN

The study is designed as a randomized, placebo-controlled, double blinded, multi-center, multi-national Phase III clinical trial, with a crossover option for all patients who have progressed.

Approximately 348 patients with newly diagnosed GBM, and with no evidence of disease progression at Baseline will be randomized 2:1 (232 into the treatment cohort and 116 into the placebo-cohort). All patients will receive standard treatment consisting of: a) surgical resection, b) external beam radiation with concurrent chemotherapy (temozolomide), and followed by additional 28-day cycles of temozolomide chemotherapy (see Appendix C for details).

Patients with evidence of progressive disease (as determined by central radiology review) post radiation therapy with concomitant temozolomide chemotherapy are not eligible for this study.

The study schedule anticipates an approximate active enrollment period of 36 months. An initial efficacy analysis for the primary endpoint (PFS) in patients with no evidence of disease progression at Baseline will be performed after approximately 248 events (progression or death) have occurred in the treated patients and the placebo controls combined, which is expected to occur approximately 5 months after enrollment of the last patient.

All patients in the study will be followed for the collection of data on late progression and vital status until a total of 233 deaths have occurred in the treatment and placebo cohorts combined, which is expected to occur approximately 36 months after completion of enrollment. Schematics of the study timeline are presented in Appendix A, and a detailed overview of the timeline following radiation therapy is provided in Appendix B.

All randomized patients receive up to 10 immunizations of DCVax-L or autologous MNC (placebo cohort) at days 0, 10, 20, and at months 2, 4, 8, 12, 18, 24 and 30) following recovery from surgery and radiation with concurrent temozolomide chemotherapy. All visits, including immunization dates, are calculated from day 0 (the date of the first immunization), and for the purposes of this protocol, a 28-day month is used for calculating visits. Some patients may not receive 10 immunizations due to insufficient material; in these cases immunizations will be replaced with placebo while maintaining the blind. Patients who elect to receive DCVax-L immunizations post confirmed disease progression and crossover will restart the immunization schedule and may receive a total of more than 10 immunizations during the course of the study.

For each immunization, patients will receive two intradermal injections (i.d.) of approximately 150µl (0.15mL) containing 1.25 million cells each (DCVax-L or MNC) in an outpatient setting. Injection volume is patient specific and the Certificate of Analysis (C of A) should be referenced. Patients are observed for acute toxicity every 30 minutes for 2 hours post-injection.

3.4. ESTIMATED ACCRUAL

It is estimated that accrual will range from 0.1 – 2 participants per month per site, at approximately 90 clinical sites participating in the study. Approximately 348 patients will be randomized into the study to test the primary and secondary hypotheses.

3.5. NAME OF SPONSOR/FUNDING SOURCE

Northwest Biotherapeutics, Inc.

4. SAFETY CONSIDERATIONS

The major component of DCVax-L is autologous DC loaded with autologous tumor lysate antigen. DC are generated by *ex vivo* culturing of adherent peripheral blood monocytes with the cytokines granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-4 (IL-4) for 5-7 days. DC are harvested, loaded with tumor lysate antigen, washed extensively, and cryopreserved as DCVax-L. After washing, only trace amounts of GM-CSF, IL-4, and unloaded antigenic material are introduced into the patient. For each immunization, two vials containing DCVax-L are thawed and two injections of approximately 150µl each are given i.d.

Autologous MNC are purified directly from a leukapheresis through density gradient centrifugation, and contain no foreign substances other than the diluent and cryopreservative.

The Phase III clinical trial is predicated on a Phase I/II clinical trial carried out at UCLA (BB-IND #11053). No Grade 3 or 4 toxicities related to the treatment were observed in this trial, leading to the preliminary conclusion that DCVax-L is safe to administer to patients with brain cancer.

There are a number of published studies referring to similar therapies that have utilized *ex vivo* manipulated autologous DC pulsed with autologous tumor lysate. No serious toxicities or clinically meaningful evidence of autoimmunity were observed in 43 trials comprising a total of 770 patients (fully referenced in accompanying Investigator's Brochure).

5. BRIEF DESCRIPTION OF MANUFACTURING PROCESS FOR DCVAX-L

Both DCVax-L and the placebo will be manufactured for all patients undergoing leukapheresis.

REDACTED

6. BRIEF DESCRIPTION OF MANUFACTURING PROCESS FOR PLACEBO

(Both DCVax-L and placebo will be manufactured for all patients undergoing leukapheresis.)

REDACTED

7. PATIENT ELIGIBILITY

7.1. INCLUSION CRITERIA

All patients, unless specified otherwise below, must meet the following inclusion criteria at the indicated time points.

Determined at pre-screening

- Patients ≥18 and ≤70 years of age at surgery
- Patients must be able to understand and sign the Informed Consent indicating that they are aware of the investigational nature of this study. The consent for tumor donation may be signed by a legally authorized representative (LAR) if allowed by the institution.
- Patients must have a life expectancy of ≥8 weeks

Determined at or around surgery, and prior to pre-leukapheresis

- Primary therapy must consist of surgical resection with the intent for a gross or near gross total resection of the contrast-enhancing tumor mass as confirmed by central review, followed by external beam radiation therapy and concurrent temozolomide chemotherapy. Patients who have a resection with original intent for gross or near gross total resection where the surgery can be said to be beyond biopsy are eligible. Central confirmation is not required prior to the pre-leukapheresis visit, but is required before the patient can proceed to leukapheresis. Patients having a biopsy only will be excluded. *Patients may be screened if they have had a previous biopsy and are scheduled for a subsequent gross or near gross total resection prior to commencement of other therapies.*
- Patients with newly diagnosed, unilateral GBM[1] (Grade IV) without metastases are eligible for this protocol. An independent central neuropathologist will review this diagnosis during the enrollment process. This confirmation is not required prior to the pre-leukapheresis visit, but is required before the patient can proceed to leukapheresis.
- All Patients must have sufficient tumor lysate protein that was generated from the surgically obtained tumor material. This determination will be made by the contracted manufacturer and communicated to the clinical site through the Sponsor, or its designee. This confirmation is not required prior to the pre-leukapheresis visit, but is required before the patient can proceed to leukapheresis.

[1] For the purposes of this study, all histologically confirmed, newly diagnosed GBM includes the recognized variants of glioblastoma (small cell glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components).

Determined at pre-leukapheresis

- Patients must have adequate bone marrow function (e.g., hemoglobin >10 g/dl or >100g/L, white blood count 3.6-11.0x10^3/mm^3 or 3.6-11.0x10^9/L, absolute granulocyte count ≥1.5x10^3/mm^3 or ≥1.5x10^9/L, absolute lymphocyte count ≥1.0x10^3/mm^3 or ≥1.0x10^9/L, and platelet count ≥100x10^3/mm^3 or ≥100x10^9/L. Eligibility level of hemoglobin can be reached by transfusion. These values are determined by a central laboratory. Note: Eligibility is maintained if these laboratory results are outside of the central laboratory's normal reference ranges or the sample ranges provided above but are not deemed clinically significant by the treating investigator.
- Adequate liver function (SGPT, SGOT, and alkaline phosphatase ≤4.0 times upper limits of normal (ULN) and total bilirubin ≤1.5 mg/dl or <25.7 µmol/L), and adequate renal function (BUN or creatinine ≤1.5 times ULN) prior to starting therapy. These values are determined by a central laboratory.

Determined at baseline

- Patients must have a KPS rating of ≥70 at the Baseline Visit (Visit 5) (refer to Appendix D, Performance Status Scales).
- Patients may have received steroid therapy as part of their primary treatment. Steroid treatment should preferably be stopped; or if continued steroid use is clinically indicated, be tapered down to no more than 4 mg dexamethasone qd at least 7 days prior to the first immunization[2].
- Patients must be willing to forego cytotoxic anti-tumor therapies except temozolomide while being treated with study drug. DCVax-L and placebo must be given as described and temozolomide must be given essentially according to the Stupp Protocol guidelines (see Appendices B and C for temozolomide schedules and detailed treatment guidelines). Administration of adjuvant temozolomide is minimally modified from the guidelines to allow for vaccine dose window adherence.
- A minimum of 5 immunizations must be available for treatment as determined by the contracted manufacturer.

7.2. EXCLUSION CRITERIA

Patients may not be enrolled in the trial if they have any of the following exclusion criteria, at the indicated time points:

Determined at pre-screening

- History of prior malignancy except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer or other cancers that were deemed fully resolved 5 or more years prior to Visit 1 (surgery) of the study. Prior lower grade gliomas are acceptable unless treated with chemotherapy, and provided that all other eligibility criteria are met.
- History of immunodeficiency disease or unresolved autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis,

[2] For all subsequent immunizations a 21-day (10 days before and after the immunization date) steroid holiday must be observed as per Section 12, Concomitant Medications

scleroderma, polymyositis-dermatomyositis, juvenile onset insulin dependent diabetes, or vasculitis.

- Known HIV-1,2, HTLV-1,2 or Hepatitis B, C infection
- Pregnancy
- Inability to obtain Informed Consent because of psychiatric or complicating medical problems.
- Any known genetic cancer-susceptibility syndromes.

Determined at or around surgery

- Bilateral or metastatic disease detected at diagnosis, during surgery or at post-surgical magnetic resonance imaging (MRI). Tumors may cross into, but not beyond the corpus callosum.
- Positive test(s) for infectious agents (HIV 1 and 2, Anti-HIV 1, 2, Hepatitis B, HVsAG, Anti HBc, Hepatitis C, Anti-HCV-Ab, Syphillis) that would preclude eligibility for tumor procurement and processing per applicable manufacturing guidelines (e.g. German manufacturing vendors).
- Post operative MRI scan evidence of biopsy only without significant tumor resection.
- Implantation of Gliadel® wafers (polifeprosan 20 with carmustine implant) at surgery.

Determined at pre-leukapheresis

- Positive HIV-1, HIV-2, HTLV-1, 2, hepatitis B surface antigen, or hepatitis C antibody.
- Patients with organ allografts.
- Allergies to reagents used in this study.
- Patients who are unable to stop or taper steroid treatment to no more than 4mg of dexamethasone qd prior to leukapheresis are excluded from the trial; steroid use should be stopped or tapered down to the lowest clinically acceptable dose approximately 7 days prior to leukapheresis[3]. The Leukapheresis Visit must occur a minimum of 45 days before the projected Baseline Visit.
- Inability or unwillingness to return for required visits and follow-up exams.
- Any previous cytotoxic drug therapies within the last 5 years.

Determined at or prior to baseline

- Patients who have evidence of disease progression (including possible pseudoprogression) as determined by central review are not eligible for the study
- Patients may not be taking medications that might affect immune function and that have documented anti-tumor activity: The following are exceptions: nonprescription strength doses of NSAIDS, acetaminophen (paracetamol) or acetylsalicylic acid (aspirin).
- .

[3] It is critical to bring steroid levels down to the lowest possible dose to maintain maximum chances of eligibility, since steroid treatment interferes with manufacturing by hampering the ability of monocytes to adhere to plastic during the purification step. Leukapheresis should occur at least 45 days prior to the projected baseline visit.

Safety considerations, determined at baseline: the following exclusion criteria preclude patients from being enrolled in the study:

- Acute infection: any active viral, bacterial, or fungal infection that requires specific therapy. Antibiotic therapy must be completed at least 7 days prior to the first immunization.
- Active uncontrolled infection. Examples are a sexually transmitted disease (STD), herpes, uncontrolled tuberculosis, malaria, etc.
- Fever ≥101.5°F (38.6 °C). If considered possibly transient, retesting is allowed.
- Unstable or severe intercurrent medical conditions such as unstable angina, uncontrolled arrhythmias, Crohn's Disease, ulcerative colitis etc.
- Females of child-bearing potential who are pregnant or lactating or who are not using adequate contraception (abstinence, surgical, hormonal or double barrier, i.e. condom and diaphragm).

8. TREATMENT PLAN

8.1. TREATMENT PLAN OVERVIEW

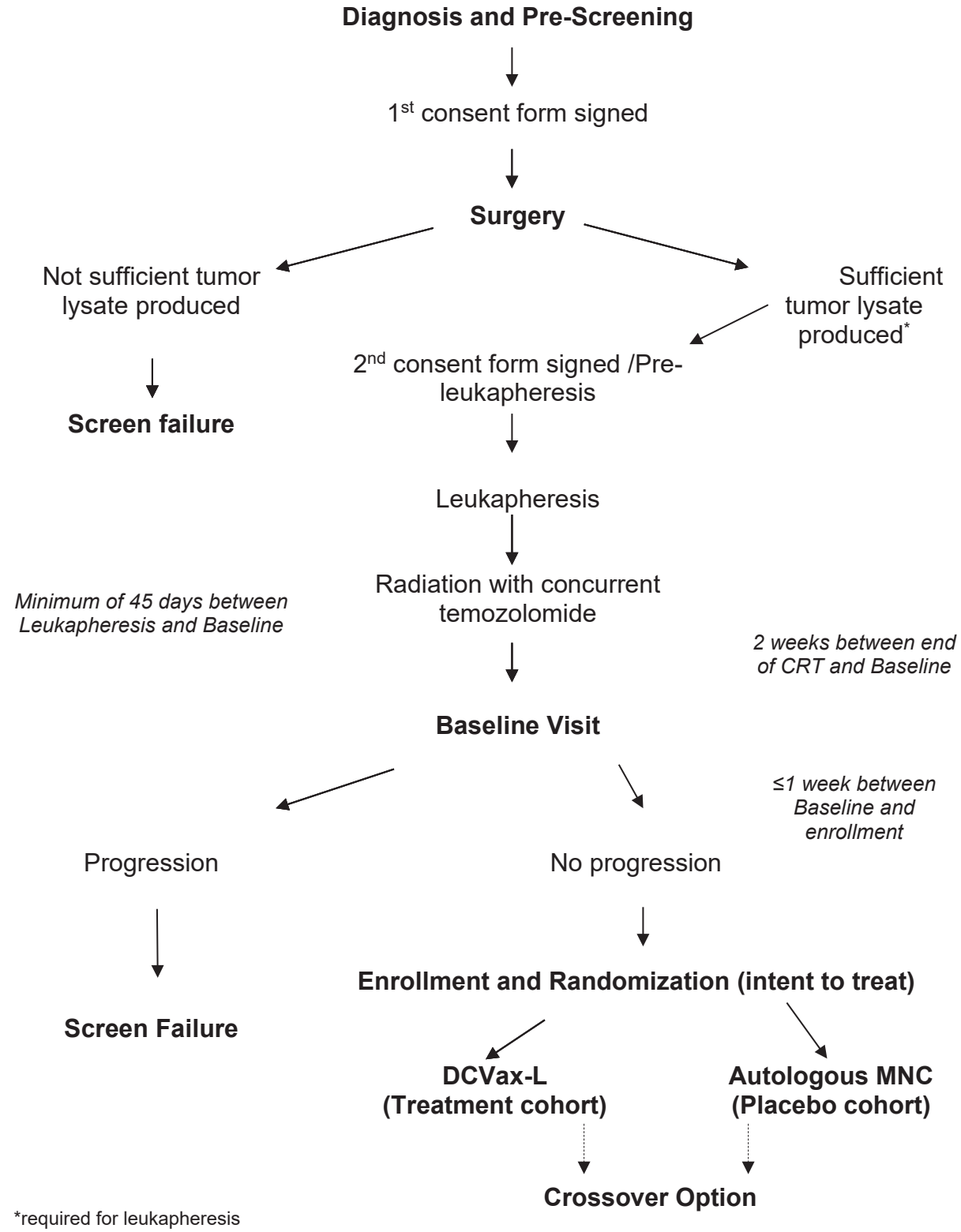
After the Informed Consent for the collection of the tumor has been signed, all subjects will undergo surgery at a center participating in the trial or at surgical centers trained in the study specific tumor processing procedure. As much as possible of the tumor material obtained from surgical resection will be placed in a sterile container and shipped to the contract manufacturer for manufacturing of the tumor lysate antigen preparation. Where applicable and per manufacturing guidelines, a blood sample for infectious disease testing is shipped with the tumor tissue to satisfy tissue procurement laws, e.g. German manufacturing vendor.

Following recovery from surgery, patients will undergo a pre-leukapheresis visit to determine viral status and bone marrow and liver function. Patients with negative viral status and adequate bone marrow and liver function proceed to leukapheresis to harvest the DC precursors, prior to initiation of external beam radiation therapy with concurrent chemotherapy. Patients for whom insufficient DCVax-L is manufactured, i.e. less than 5 doses, will be eligible to undergo additional apheresis if it is determined that the leukapheresis can be completed and DCVax-L manufactured and released prior to the Baseline Visit (approximately 44 days). Peripheral blood mononuclear cells (MNC) are purified from the leukapheresis material at the contracted manufacturer, and an aliquot of the MNC is cryopreserved for use as placebo for patients who are randomized to the placebo cohort. The remainder of the MNC is used to prepare DCVax-L. Both DCVax-L and the placebo are tested at the contracted manufacturer prior to release to the study site. Patients for whom sufficient DCVax-L was not generated are not eligible to continue on this protocol.

All subjects who had a leukapheresis will undergo external beam radiation therapy (which may include intensity modulate radiation therapy or IMRT) and concurrent temozolomide chemotherapy as part of standard primary treatment, initiated as soon as possible, typically 3-4 weeks after surgery (Appendices A & B). If a subject starts radiation and chemotherapy treatment prior to leukapheresis, there must still be a minimum of 45 days between leukapheresis and the projected Baseline Visit to allow for the manufacture of study vaccine.

Two weeks after completion of radiation and concurrent chemotherapy treatment, subjects will undergo the Baseline Visit, during which the final tests to determine eligibility are performed. Patients who do not have evidence of progressive disease at the Baseline Visit (as determined by central read of MRI) are enrolled in the study (intent to treat), and are randomized to receive DCVax-L in the treatment cohort or autologous MNC in the placebo cohort. Randomization and treatment assignment takes place within 1 week of the Baseline Visit. At the Baseline Visit, patients must be scheduled to return to the clinic approximately 1 week later to receive their first immunization. The study drug, containing approximately 2.5 million DC per immunization (two injections of 1.25 million DC each per immunization, in approximately 150 μl each), is injected i.d. (not subcutaneously) into a clean area of the upper arm, alternating arms between visits. Injection volume is patient specific and the Certificate of Analysis (C of A) should be referenced.

Table IV. Treatment Schedule Overview
(Detailed authoritative schedule provided in Appendices A and B).



*required for leukapheresis

8.2. SCREENING PROCESS

Pre-Screening: The following parameters should be established prior to entering the screening process: age (must be in range), absence of prior malignancies (within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer) and no known unresolved autoimmune disease, HIV-1,2 or Hepatitis infection, no known genetic cancer-susceptibility syndromes, or known pregnancy. If these conditions are satisfied, patients are entered into the screening process by signing the first Informed Consent form.

Visits 1-3 (see Appendix A) are used to screen patients for initial eligibility for the trial. The tests and assays performed at the following visits determine eligibility:

Visit 1 (Surgery): All patients (or their LAR) will sign an Informed Consent form to allow collection of the tumor and perform study activities required for screening. The surgical intent should be a total or near total resection.

Collection of tumor tissue: all available tumor tissue should be collected to maintain maximal chances for eligibility. Determination of eligibility is based on the amount of tumor lysate protein recovered rather than on the amount of tumor tissue submitted. Where applicable and per manufacturing guidelines, a blood sample for infectious disease testing is shipped with the tumor tissue to satisfy tissue procurement laws, e.g. German manufacturing vendor.

All patients must have newly diagnosed, unilateral GBM without metastases. All pathologic diagnoses of GBM will be reviewed by independent pathology review.

As soon as possible following surgery, slides for independent pathology confirmation of the GBM diagnosis as well as slides for determination of MGMT methylation status should be sent in. In some cases, the MGMT methylation status will be determined as part of standard care at the institution. If it is confirmed that the MGMT methylation status is evaluated at an accredited laboratory, the available lab result may be used. MGMT methylation status is a predictive factor for temozolomide responsiveness[4], and is used for stratification of the randomization.

Visit 2 (Post-surgery MRI): MRI scans pre- and post-surgery need to document extent of resection beyond biopsy only. Patients must have a surgically accessible tumor for which surgical resection, with intent to perform a gross total or near gross total resection, is indicated. Biopsy only does not satisfy eligibility rules. MRI scan (post-surgical) must demonstrate that a resection was performed beyond biopsy only. All MRI scans will be reviewed by central independent radiology review.

The post-surgery MRI will be used to quantitatively determine the extent of resection for purposes of the statistical analyses in section 13.2.3 and 13.3.3. Extent of resection will be defined as the amount of residual tumor volume measured in mm^3.

The amount of tumor lysate protein is determined as soon as possible after surgery by the contract manufacturer. Determination that sufficient tumor lysate protein was generated is required for a patient to remain eligible and to undergo leukapheresis.

[4] Hegi, ME et al. 2005. N Engl J Med. 2005 Mar 10;352(10):997-1003.

Patients may have received steroid therapy as part of their primary treatment. Steroid treatment should preferably be stopped, but if continued steroid use is clinically indicated, be tapered down to the lowest acceptable dose (i.e. no more than 4 mg dexamethasone qd) approximately 7 days prior to leukapheresis to secure the highest possible quality of the cells used for DCVax-L manufacturing.

Visit 3 (Pre-leukapheresis): Just prior to proceeding to leukapheresis, patients are assessed for viral status and bone marrow and liver function. The following tests and procedures are done at the pre-leukapheresis visit:

- Sign study Informed Consent Form (second Informed Consent)
- History
- Pregnancy test
- Hematology: CBC, differential, platelets
- Virology testing: HIV-1, 2, HTLV-1,2, Hepatitis B, C
- Serum Chemistries: calcium, SGOT, SGPT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, electrolytes, magnesium and glucose
- Urinalysis: normal routine urinalysis

Collection of AE and concomitant medications begins at Visit 3.

Visit 4 (Leukapheresis): Patients proceed to leukapheresis as soon as they are sufficiently recovered from surgery, the second Informed Consent Form is signed and after continued eligibility has been determined (unilateral GBM and resection beyond biopsy confirmed, GBM diagnosis confirmed, sufficient tumor lysate generated, negative viral status, adequate bone marrow and liver function, steroid taper). It is recommended but not required that patients complete leukapheresis prior to starting chemotherapy and radiation. An absolute minimum of 45 days is required from the date of leukapheresis to the Baseline Visit.

Visit 5 (Baseline): Visit 5 takes place 2 weeks (± 2 days) after the last day of radiation therapy with concurrent temozolomide chemotherapy. A minimum of 5 immunizations must be available for treatment as determined by the contracted manufacturer. At the Baseline Visit, the patient undergoes AE assessment, an MRI to assess disease progression and blood draws to assess eligibility.

Patients who have evidence of disease progression (measured by MRI, compared with post-surgery MRI and verified by independent review), are not eligible for this study. Patients who do not have progressive disease at baseline are enrolled in the study, and will be randomized to receive DCVax-L or placebo at a 2:1 ratio. All remaining inclusion and exclusion criteria must be met for all patients to be enrolled.

The following tests and examinations are to be performed at Baseline (Visit 5):

- MRI with and without contrast of the brain to confirm absence of disease progression (verified by independent radiology review)
- Physical Examination
- Neurological Exam
- Vitals

- KPS
- CBC and differential, Blood chemistry
- Pregnancy test: Serum hCG pregnancy test is performed on female subjects of child bearing potential
- Anti-DNA antibodies as a marker of autoimmune disease. Results from this test are not required prior to immunizations
- AE assessment

Eligibility to be enrolled in the study will be determined on the basis of the outcome of these tests, which are to be evaluated within the shortest possible time after the Baseline Visit (target <1 week for confirmation of eligibility) to ensure earliest administration of DCVax-L.

8.3. ENROLLMENT AND RANDOMIZATION

In order for a patient to be enrolled in the study, they must meet all eligibility criteria above, including absence of disease progression following radiation with concurrent temozolomide chemotherapy. Absence of disease progression must be confirmed by central independent review of the post radiation MRI performed at the Baseline Visit (Visit 5), compared to the post-surgery MRI.
The patients meeting these criteria are enrolled, and immediately randomized into the treatment cohort or the placebo cohort of the study (enrollment and randomization happen concurrently). Final review prior to enrolling and randomizing a patient into the trial will be made by the Sponsor and the outcome will be communicated to the clinical site.

8.4. CROSSOVER (OPEN LABEL) ARM

Patients enrolled in the study for whom disease progression is established at any point after randomization (as defined in section 15.2 of this protocol, and verified by independent review) will be offered the opportunity to receive DCVax-L and/or any other established treatment of the physician's choice. All procedures below should be followed. Patients who do not participate in the crossover option of the study will return for an EOT visit and continue to be followed for survival.

Study Procedures for Crossover (Open Label) Option:
Patients who, wish to continue in the study after confirmation of disease progression, will have the option to receive DCVax-L under the crossover/open label arm of the study (except in rare cases where they were originally randomized to DCVax-L and have exhausted their supply). Patients enrolled into the crossover arm will be required to follow the same study visit schedule as patients enrolled into the treatment arm of the study (Appendix A1). Patients may be treated with any additional established therapies. For these patients, the **Guidelines for Combination Therapy Approaches** described below should be referenced.

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Immune Monitoring

- Immune monitoring samples will not be drawn for patients enrolled in the crossover study arm

Labs:

Labs will be collected prior to the first immunization of a patient following crossover. A negative urine pregnancy test must be obtained for all female subjects of child bearing potential prior to receiving the immunization.

For all scheduled lab tests during treatment with DCVax-L, central laboratories will be used. Prior to the first immunization of a patient following crossover, the following samples will be collected for the central lab (but results are not required prior to immunization):

- CBC and differential
- Blood chemistry - Comprehensive metabolic panel, including electrolyte balance, and hepatic and renal functions
- Serum hCG for pregnancy
- Anti-DNA
- Urinalysis
- All scheduled and unscheduled MRI and other radiographic images should be sent to central radiology for independent review

Clinical Drug Supply:

- Clinical Drug Supply vendor is notified that a patient has confirmed disease progression. Refer to the study reference manuals for further details. The drug manufacturer is notified of the crossover by the Sponsor or its designee.

Treatment Schedule after Confirmed Progression and Crossover

- Patients will receive up to 10 DCVax-L injections at days 0, 10, 20, and months 2, 4, 8, 12, 18, 24 and 30. Day 0 is the date of the first immunization and must occur within 3 months of crossover (date of confirmation of disease progression). For the immunizations at days 10 and 20, and month 2, the variance may be ±2 days but the minimum interval between injections must be at least 9 days. For the immunizations at months 4, 8, 12, 18, 24, and 30 the variance can be ±1 week with a minimum interval of 6 weeks between injections. Vitals are recorded every 30 minutes for 2 hours post injection.

Guidelines for Combination Therapy Approaches:

If chemotherapies other than temozolomide are combined with DCVax-L following crossover, the following guidelines are recommended. Deviations from these guidelines during the Crossover phase of the trial do not constitute protocol violations.:

- A 21 day window surrounding DCVax-L immunizations (10 days before and 10 days after the day of vaccination), during which no chemotherapies (with the exception of temozolomide) should be given, is recommended;
- Keeping the corticosteroid dose as low as tolerated within the 21 day window around vaccine administration is recommended.

Treatment Schedule and Procedures:

Follow the schedule of events outlined in Appendix A1, and in Section 8.1 of this protocol as appropriate within the patient's treatment plan.

Treatment Discontinuation Due to no Study Drug Availability:

- If the crossover patient is receiving DCVax-L and no more study drug is available, the patient will discontinue from active treatment, have an End of Treatment (EOT) visit as per Section 8.5, and will be followed for survival. Follow-up will be conducted through quarterly phone calls per Sections 11 and 15.4 and Appendix A/A1 footnotes of the protocol.
- An explanation for discontinuing treatment is recorded for each patient on the appropriate CRF/eCRF.

8.5. END OF TREATMENT (EOT) VISIT SCHEDULE AND PROCEDURES (ALL PATIENTS – RANDOMIZED AND CROSSOVER):

EOT Visits for all patients who discontinue from the study should occur at least 7 days, but ≤ 30 days, after the last immunization and prior to beginning other treatment. Procedures to be performed during the EOT Visit include:

- Physical Exam
- Neurological Exam
- Vital Signs
- KPS
- MRI of brain
- CBC and Differential
- Blood Chemistry - Comprehensive metabolic panel, including electrolyte balance, and hepatic and renal functions
- Serum markers of Autoimmune disease (anti-DNA)
- Urinalysis
- AE Assessment
- Concomitant Medication

8.6. EMERGENCY UNBLINDING PROCEDURES

- Site to contact the Medical Monitor
- Upon review and approval by the Medical Monitor the patient may be unblinded.
- **It is important that only the Investigator be unblinded. The patient and all other personnel are to remain blinded including NWBT and the CRO personnel**
- CRAs who become cognizant of the unblinded information during monitoring visits are not permitted to share this data with others to ensure that aggregate treatment assignment data cannot be assembled prior to the scheduled endpoint analyses

8.7. ADMINISTRATION OF DCVAX-L OR PLACEBO

Over the course of the study patients will receive up to 10 DCVax-L or placebo injections at days 0, 10, 20, and at months 2, 4, 8, 12, 18, 24 and 30. Some patients

may not receive 10 immunizations due to insufficient material. Patients who have exhausted all doses of DCVax-L are switched to placebo. This switch will not be communicated to the patient or physician to maintain blinding.

For injections at day 0, the variance may be +2 days. For injections at days 10, 20 and at month 2, the variance may be ±2 days but the minimum interval between injections must be at least 9 days. Thereafter, the variance can be ±1 week with a minimum interval of 6 weeks between injections. All visits, including immunization dates, are calculated from day 0 (the date of the first immunization), and for the purposes of this protocol, a 28-day month is used for calculating visits.

Immunizations can be delayed by up to 2 weeks for visits prior to month 8, or by up to 4 weeks for the Month 8 visit and each visit thereafter. These delays are in addition to the already allowed window, to accommodate unforeseen circumstances. If such a delay is incurred, the immunization schedule should thereafter be resumed as originally planned (as calculated from Time 0).

Examples of reasons that are allowed for the above referenced delay include:

- Acute illness from which the patient recovers in time to incur no more than the allowed delay for the next scheduled visit;
- A temporary need for high dose steroids or other complications from the disease under study;
- Outside acts that prevent the patient from travelling;
- Other unavoidable circumstances outside of the patient's control.

At the clinical site, just prior to drug administration, the shipper is opened and two vials of DCVax-L or placebo are removed and patient identifiers are verified. The vials are thawed at room temperature and the contents are drawn into an insulin syringe with minimal dead space to deliver a total of 2.5 million tumor lysate antigen-loaded DC (DCVax-L) or autologous MNC (placebo). Injection volume is patient specific and the Certificate of Analysis (C of A) should be referenced. It is preferred that these procedures are performed at a clinical or investigational pharmacy. Study drug should be administered as soon as possible after thaw; no more than 30 minutes should elapse between thawing and administration. For each immunization, two separate i.d. injections of approximately 0.15 mL (150 ul) each are given in the upper arm (alternating arms at each treatment visits). If subcutaneous injection occurs, this should be recorded on the eCRF, and the injection SHOULD NOT be repeated. The patient is observed for 2 hours after administration of each injection with vitals (heart rate, respiration rate, and blood pressure) taken pre-injection and every 30 ± 5 minutes and only recorded (as AEs) if considered clinically significant.
Because post-injection anaphylactic reactions to DCVax-L or any of its components cannot be fully precluded to occur on the study, facilities for resuscitation must be available when administering DCVax-L or placebo.

9. PATIENT EVALUATION

9.1. ON-STUDY CLINICAL EVALUATIONS

Clinical evaluations take place according to the Schedule of Events (Appendix A). Follow-up visits should be scheduled to occur once every two months, ±7 days for vaccination visits and ±14 days for all other study visits. For this purpose, all visits after

month 2 are considered follow-up visits. The window between these visits should be as close to 2 months as possible, no less than 6 weeks, and no more than 12 weeks. The following tests and procedures are completed, although not all tests may be done at each visit; see the detailed study timeline in Appendix A.

- Physical Examination
- Neurological Exam
- Vitals (every 30 minutes for 2 hours post injection)
- KPS
- MRI of brain with and without contrast every 2 months ±2 weeks, with a minimum of 6 weeks between scans
- Hematology: CBC, differential, platelets
- Serum Chemistries: including calcium, magnesium, SGOT, SGPT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, electrolytes, and glucose
- Serum markers of Autoimmune disease (anti-DNA)
- Immune monitoring (Immune monitoring samples will not be drawn for patients enrolled in the crossover study arm)

9.2. IMMUNOLOGICAL STUDIES

The immunological studies that are intended for this clinical trial are initially exploratory in nature. Future expansion of these studies to determine immunological correlates for clinical efficacy may be undertaken based on initial results.

For all patients, until they crossover, blood will be obtained and MNC harvested and stored for future analysis. The following tests for monitoring the immune response to DCVax-L may be used for this study. Refer to Appendix A for the timing of these blood draws.

- Mixed lymphocyte-DCVax-L culture
- Cytokine release (e.g. through Elispot)
- Immunohistochemical staining of resected brain tissue upon recurrence may be undertaken in a separate study

Feasibility

Some of the above assays (mixed lymphocyte-tumor cell cultures, cytokine release) are dependent on the availability of DCVax-L material in excess of what is required for treatment. Excess material will not be available for all patients and it may not be available for any patients. Assays will therefore be limited based on the amount of available material.

9.3. ADDITIONAL INVESTIGATIONS

New information has elucidated the existence of various immune profiles as well as genetic tumor variants in GBM, and the prognostic implications of these profiles and variants. For all patients, immune status and profile, genomic profile and other analyses of tumor tissue that was collected at initial surgery and at subsequent surgeries, and biologic samples that were collected throughout the trial and stored for

subsequent analyses will be conducted to determine factors that may be related to trial endpoints, including but not limited to:

- IDH-1/2 mutational status
- PTEN mutational status
- EGFR amplification status
- Chromosome 1p19q deletions
- GBM subtypes: Classic, proneural, neural, mesenchymal
- Other genomic analyses

Additional assays will include tests related to immune status of the patient and of the tumor, including Immunoscore®, PD-1/PD-L1 expression status, expression of other immune related genes such as cytokines and costimulatory molecules, and infiltration of immune cells into the tumor.

These assays are dependent on the availability of material in excess of what is required for diagnosis. Excess material will not be available for all patients, and assays may therefore be limited based on the amount of available material. Additional tests to identify new prognostic or predictive markers may also be conducted.

10. TOXICITY MONITORING

Both acute and chronic toxicities are recorded and reported to the Sponsor, or its designee, and will be reviewed by the independent DMC at scheduled meetings. Monitoring for acute toxicity takes place during and immediately following injection for a period of 2 hours at the study site. Patients are observed for the development of an immediate localized allergic reaction or anaphylactic reaction during this time. Chronic toxicity is evaluated at the bi-monthly physical examination and by scheduled clinical laboratory tests.
Brain edema is common in patients with glioblastoma and could hypothetically be exacerbated upon DCVax-L treatment. Patients should be under surveillance for signs of edema and steroid treatment as allowed per Section 12 may be applied at the investigator's discretion.

11. PATIENT DISCONTINUATION OF ACTIVE TREATMENT

An explanation for discontinuing treatment is recorded for each patient discontinuing treatment on the appropriate CRF/eCRF. The Sponsor, or its designee, must be notified immediately if a patient discontinues treatment. All patients, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- if the Sponsor decides to stop the study;
- at Investigator's discretion;
- at the patient's request;
- if the patient enrolls in a trial of another investigational agent for the treatment of GBM;
- Grade 4 or life-threatening toxicity (See Section 11, Adverse Events) attributable to DCVax-L;
- injection site reactions of Grade 3 or higher, according to the grading in Appendix E, Modified Grading of Injection Site Reaction Toxicity;
- development of clinical signs and symptoms of autoimmune disease;
- pregnancy;

- development of an allergic reaction of Grade 2 or higher, with exception of transient (<1 hour) fever or other constitutional symptoms, localized urticaria, and transient (<30 seconds) shortness of breath, or immunological reaction Grade 3 or higher to DCVax-L, with the exception of low grade fever of <39ºC (102.2 ºF) which resolves spontaneously or with antipyretics within 48 hours.

12. CONCOMITANT MEDICATIONS

Medications and therapies taken by the patients, starting at the Pre-Leukapheresis Visit (Visit 3) and continuing throughout the study are recorded on the appropriate CRF/eCRF. Limitations on use of concomitant medications during this period are listed below.

- Patients may take small amounts of topical or inhaled corticosteroids, as well as corticosteroids used as replacement therapy for adrenal steroids, e.g., <0.75 mg of dexamethasone, or equivalent.
- Due to interference with immune function, it is strongly recommended that adrenal steroids (>0.75 mg) not be used during the 21-day time window that starts 10 days before and ends 10 days after each DCVax-L immunization. If steroid therapy is clinically indicated, doses should be kept as low as possible, (for example, 2 mg per day).
- Patients may take doses of nonprescription strength NSAIDS, acetaminophen (paracetamol), ibuprofen or acetylsalicylic acid (aspirin) for non-chronic headache, muscle pain, trauma or prophylaxis as long the dosing regimens comply with the recommended dose in the product labeling.
- Patients may receive antihistamine therapy for colds or allergies at non-prescription doses, but patients should not take these medications within 5 days before or after an immunotherapy injection.
- Patients may take vitamin supplements within a dose range not associated with toxicity.
- Patients may take cimetidine or other H_2 blockers.
- Other treatments and medications that may affect immune function, that have known or suspected anti-tumor activity, or that could interfere with the imaging assessment of disease progression are not allowed for patients prior to crossover. A list that gives examples of such therapies is included in the study manual.
- The use of other investigational agents is not permitted.
- Active immunotherapy is not allowed for any patient.
- Administration of adjuvant temozolomide is minimally modified from the Stupp protocol schedule guidelines for treated patients to allow for vaccine dose window adherence and avoid interference with DCVax-L immunizations. See Appendices B and C for details. Temozolomide should not be given during the window described as 1 (one) day before and preferably ≥ 7 days after DCVax-L/Placebo administration.

13. ADVERSE EVENTS

13.1. TISSUE PROCUREMENT RELATED ADVERSE EVENT RECORDING (GERMAN MANUFACTURING ONLY)

Adverse reactions related to the procurement and/or processing of the tumor tissue and leukapheresis product must be reported to the manufacturer of DCVax-L, when manufacturing occurs in Germany per German Drug Laws. Reporting instructions will be available in the manufacturing guidelines where applicable.

A serious incident is any undesired event in connection with the harvesting, testing, processing, preserving, storage or supply of tissues or blood preparations which could lead to:

- The transmission of an infectious disease,
- Death of a patient,
- A life-threatening state, disability or invalidity of patients,
- Need for hospitalization or prolongation of hospitalization
- Causes or prolongs a disease
- Medically important event

A serious adverse reaction is an unintended reaction, including an infectious disease in the donor or recipient in connection with the harvesting of tissues or blood or the transplanting of tissue or blood preparations, which is:

- fatal or life-threatening, or
- leads to disability or invalidity, or
- requires hospitalization or the prolongation of existing hospitalization,
- or causes or prolongs a disease.

13.2. ADVERSE EVENT RECORDING

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug and from any route of administration, formulation, or dose, including an overdose.

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility (evidence to suggest a causal relationship) that the drug caused the adverse event.

An adverse reaction is defined as a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

AEs are collected after signing the study Informed Consent Form (second Informed Consent) at the pre-leukapheresis visit. AEs may include a single symptom or sign, a set of related symptoms or signs, or a disease while receiving the study drug. All AEs must be recorded and reported in the CRF/eCRF, irrespective of relationship to study drug.

Patients are instructed to report any AE to the Investigator. On each day of evaluation, the patient is questioned regarding any new medical problems and new or changed medications. All AEs are documented in the source document and on the AE Form (located in the CRF/eCRF).

The intensity of all AEs not localized to the injection site of the study drug is graded according to the U.S. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTC) version 3.0 (Appendix F). AEs that are considered by the Investigator to be localized or related to the injection site shall be graded according to Modified Grading of Injection Site Reaction Toxicity (Appendix E).

The relationship of an AE to study treatment is characterized as “not related”, “unlikely related”, “possibly related”, “probably related”, or “definitely related” and is determined by the Study Center physician/Principal Investigator (PI) according to the following guidelines:

- **Not Related**: The adverse event is clearly not related to the study drug and is clearly related to an underlying disease, environmental or toxic factors, or other drug/therapy.
- **Unlikely to be Related**: The adverse event does not follow a reasonable temporal sequence after study drug administration (e.g., too soon or too long after study drug or study drug was not taken) and is plausibly related to an underlying disease, environmental or toxic factors, or other drug/therapy. Events assessed “not likely” related will be considered unrelated to study drug.
- **Possibly Related**: The adverse event occurred in a reasonable time after study drug administration but could be related to an underlying disease, environmental or toxic factors, or other drug/therapy. There is a reasonable possibility of a causal relationship between the study drug and the adverse event.
- **Probably Related**: The adverse event occurred in a reasonable time after study drug administration and is unlikely to be related to an underlying disease, environmental or toxic factors, or other drug/therapy. The event may respond to stopping the study drug.
- **Definitely Related**: The adverse event occurred in a reasonable time after study drug administration but could not be explained by an underlying disease, environmental or toxic factors, or other drug/therapy. The event should respond to stopping the study drug.

The expectedness of the event will also be evaluated. An AE 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 an Investigator 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. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater severity) if the Investigator 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 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.

Study-Specific Adverse Event Recording

- The time period for AE assessment starts at pre-leukapheresis through 30 days after the patient exits from participation in the trial (off study date) or last study treatment, (whichever comes later). It is recognized that the date the patient is determined to be “off-study” may not coincide with a visit date. ;
- Newly emergent symptoms or worsening of existing symptoms of underlying disease (GBM) should be reported as AEs;
- AEs due to disease progression should be reported as the actual signs or symptoms, rather than “disease progression”

- Radiographically detected disease progression and ensuing surgery and hospitalization in the absence of clinical symptoms does not classify as an AE;
- Abnormal laboratory values are AEs only if deemed “clinically significant” by the Investigator; “clinically significant” in this context could include:

  a.) leading to a change in treatment or other study procedures, or

  b.) requiring intervention.

13.3. SERIOUS ADVERSE EVENT REPORTING

A Serious Adverse Event (SAE) is defined as, if in the view of either the Investigator or Sponsor, an adverse event or suspected adverse reaction results in one of the following outcomes:

- death;
- an event that is life threatening (places the patient at immediate risk of death);
- an event that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- an event that requires inpatient hospitalization or prolongs hospitalization;
- an event that is a congenital anomaly/birth defect;
- an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

It is anticipated that progressive disease will occur and symptoms from this may well constitute an SAE. The symptoms of progressive disease are considered expected events.

13.4. RECORDING AND FOLLOW-UP OF ADVERSE AND SERIOUS ADVERSE EVENTS

All AEs that occur (or that worsen from pre-leukapheresis status) from pre-leukapheresis through 30 days after the patient exits from participation in the trial or last study treatment, (whichever comes later), will be recorded. Adverse events that occur after enrollment but before the first immunization will be considered not related to study drug. Duration, severity, and outcome for each AE will be recorded on the CRF/eCRF Adverse Event Form, and treatment administered for the event will be recorded on the Concomitant Medications pages; this information must also be recorded in the source documentation. Adverse events will be followed until resolution, until no further improvement is expected, or until the patient is lost to follow-up, whichever comes first.

- SAE will be recorded on the Serious Adverse Event Form, which will be faxed or e-mailed to the Sponsor, or its designee, indicated in the study manual within 24 hours of becoming aware of the event. A corresponding AE must be recorded in the source documents and the eCRF.
- All SAE must be followed until the event has resolved, until no further improvement is expected, or until the patient has been lost to follow-up, whichever comes first.
- AE beginning more than 30 days after the last treatment, that the Investigator considers related to study treatment, will be reported to the Sponsor or its designee, indicated in the study manual at any time such events occur.
- Toxicities that were present at the study start and that worsen during the study should be reported as beginning on the date the event worsened, not the date it began pre-study. Event text may include the word “worsened” or “exacerbated.”

- *All AEs are documented in the source document and on the AE Form (located in the CRF/eCRF).* ***The intensity of all AEs*** *not localized to the injection site of the study drug* ***is graded*** *according to the U.S. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTC) version 3.0 (Appendix H).*
  http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf
- ***Grade*** *refers to the* ***severity*** *of the AE. The CTCAE v3.0 displays Grades 1 through 5 with* ***unique clinical descriptions of severity for each AE*** *based on this general guideline:*
  Grade 1 Mild AE
  Grade 2 Moderate AE
  Grade 3 Severe AE
  Grade 4 Life-threatening or disabling AE
  Grade 5 Death related to AE
- For AEs collected throughout the NWBT 020221 study, please use the **CTCAE *guideline to GRADE the severity of AEs***, and report the event term by medical diagnosis. If the chosen event term is not found in the CTCAE then use a similar term for guidance or refer to the general definitions provided above.

- Pregnancies occurring during the study will be followed until resolution (termination or 3 months after birth). Pregnancies should not be recorded as an AE but a Pregnancy Report Form should be completed and forwarded to the SynteractHCR team (USA) or PAREXEL GPPG (outside the USA) within 24 hours of learning of the pregnancy. The pregnancy information will be forwarded to NWBT within 2 business days. The pregnancy will be processed within SAE timelines only if the pregnancy is associated with an SAE. Note, any congenital anomaly/birth defect in a child born to a female participant should be reported as an SAE. Follow–up must be performed every three months until pregnancy termination or until three months after child birth.

13.5. EXPEDITED REPORTING OF SAE

All SAEs that occur from pre-leukapheresis through 30 days after the patient exits from participation in the trial or last study treatment, (whichever comes later), are immediately reportable to the Sponsor, or its designee, regardless of relationship to study treatment. A Serious Adverse Event Report Form must be completed and sent to that contact by facsimile within 24 hours of becoming aware of the event. Additionally, if there is any suspected relationship to the leukapheresis procedure or the study drug administration, the Sponsor or Sponsor's designated contact listed in the study manual should be notified by telephone within the same 24 hours. A narrative from the Investigator, outlining the details of the AE, its treatment, and its outcome is to be included on this form. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event should be submitted only for SAEs deemed at least possibly related to study drug or study procedures such as blood draws, leukapheresis, or study drug injections, with a revised Serious Adverse Event Report Form as soon as the information becomes available.

Northwest Biotherapeutics is required by regulatory agencies to report all serious and unexpected AE that are possibly, probably, or definitely related to the use of the study drug in clinical studies in an expedited manner. Therefore, Investigators are required to provide timely completion and follow-up of the Serious Adverse Event Form.

In the event that a serious unexpected suspected adverse reaction (SUSAR) is reported, as required by local regulatory authorities, the Sponsor or designee may ascertain the treatment assignment and unblind the patient to assess the need for expedited reporting to a regulatory authority. The treatment assignment will only be known by necessary Sponsor employees/consultants, or designees for the purpose of regulatory reporting. Procedures for unblinding are found in section 8.6 and will be described in the study manual and IXRS manual.

In addition to notifying the Sponsor's designated contact listed in the study manual of SAE, Investigators are required by US regulations as described in *21 CFR §312.66 (Assurance of IRB Review)* and EU safety reporting guidelines, to notify their Competent Authorities (CA) and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly of all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that the Investigator will not make any changes in the research without CA/IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. This means that the Investigator will report to the CA/IRB/EC all SAE occurring at the Investigator's study site(s). In addition, Investigators are also required to report to their CA/IRB/EC all SAE that are immediately reportable to this study (i.e., Expedited Safety Reports/SUSARs), regardless of when the SAE occurred. In these situations, the Sponsor or its designee will provide the necessary information to the Investigator to report to their CA/IRB/EC in the form of an Expedited Safety Report Letter.

14. POSSIBLE RISKS AND SIDE EFFECTS; SPECIAL MONITORING DURING INVESTIGATIONAL STUDIES

Some patients may expect to have local injection site reactions. Local reactions consist primarily of mild to moderate pain at the injection site, rash, pruritus, induration, tenderness, vesiculation, abscess formation, ulceration or necrosis at the site of injection, and/or regional lymphadenopathy.
Serious systemic reactions to attributed to DCVax-L have not been observed to date. Mild fever or fatigue has been observed in patients injected with DCVax-L. Systemic reactions may include the following symptoms: sneezing, coughing itching, shortness of breath, abdominal cramps, vomiting, diarrhea, tachycardia, hypotension and respiratory failure in severe cases. Systemic allergic reactions including anaphylaxis must be immediately treated with Epinephrine HCL 1:1000.
The risks to newly diagnosed GBM patients as a result of intradermal (i.d.) administration of DCVax-L in the clinical trial may include the following:

- Fatigue, fever, nausea, vomiting, and citrate toxicity secondary to leukapheresis. Leukapheresis. Leukapheresis procedures for blood collection are well established and controlled.
- Fatigue, fever, nausea and vomiting secondary to treatment of the DC with Leukine® or IL-4. After the culture period the DC are washed vigorously to remove residual Leukine® and IL-4, thus minimizing adverse toxicity.

- Administration of DCVax-L may result in local reactions at site of injection resulting in discomfort, bruising, and/or skin ulceration.
- Administration of DC loaded with cell lysate, such as tumor cell lysate, could theoretically cause autoimmunity due to the presence of self-antigens. However, no signs of autoimmunity were observed in the clinical trials with DCVax-L or other related products in altogether more than 1100 patients (see also sections 2.2 and 4).

Furthermore, patients with GBM, irrespective of their immunization status with DCVax-L, are expected to experience symptoms arising from progression of their disease, which may include any or all of the following: headaches, seizures, motor dysfunctions, speech problems, sensory disturbances, altered consciousness, and other sequelae of brain cancer.

15. CRITERIA FOR ENDPOINT EVALUATIONS

Disease progression is assessed by MRI, including T1, T2 and FLAIR sequences. All images are subject to independent central review following a prospectively formulated review charter.

15.1. DISEASE ASSESSMENT PRIOR TO ENROLLMENT

The following criteria are used to determine disease status at the Baseline Visit. If the patient does not demonstrate disease progression based on the criteria below, the patient will be deemed eligible for enrollment in the trial. If disease progression is determined, the patient will not be randomized into the trial.

- In the case of complete resection during primary therapy, there is a new, measurable tumor at the site of the resected tumor (mass greater than 1 cm [10 mm] on MRI).
- In the case of incomplete resection during primary therapy, there is a ≥ 25% increase in the residual tumor and the recurrent portion of the tumor is at least 1 cm in its longest diameter.
- There is appearance of a new lesion/site at least 1 cm in at least 1 dimension or greater, as measured by MRI at a location separate from the original resected tumor.

15.2. DEFINITION OF PROGRESSION AFTER ENROLLMENT

Progression, calculated from the nadir tumor burden (i.e. post operative orBaseline), is defined as one of the following:

- In the case of complete resection during primary therapy: a new measurable tumor at the site of the resected tumor, defined as a mass with a longest diameter equal to or greater than 1 cm in at least one dimension. If progression is not defined by these studies, treatment may proceed and determinations made at the next scheduled MRI.
- In the case of incomplete resection during primary therapy: a 25% increase or greater in the residual tumor if the recurrent portion of the tumor is at least 1 cm or greater in its longest diameter, measured by MRI and confirmed by scans above as attributable to tumor growth;
- If resection is indicated for recurrent disease, while radiographic criteria for progression have not been met: surgical resection, subsequently confirmed as

progressive GBM by Pathology at the clinical site and to be confirmed by independent pathology;

- Appearance of any new lesion/site at least 1 cm in at least one dimension or greater measured by MRI and confirmed by scans above;
- Unequivocal progression of non-measurable disease (either non-enhancing disease seen only on T2/FLAIR images or enhancing disease not meeting size criteria for measurability), such that there is confidence that tumor growth has occurred;[5]
- Death: all deaths are counted as events for the primary endpoint.

Radiographic evidence of disease progression will be evaluated and corroborated by independent radiology review to determine disease progression for purpose of this trial. MRIs to assess disease progression are done every 2 months. Unscheduled MRIs or other testing will be recorded in CRFs/eCRFs. If, during unscheduled procedures, there is evidence of disease progression, it must be confirmed through independent review as described above.

15.3. DEFINITION OF CONFIRMED PROGRESSION AFTER ENROLLMENT

For purposes of the new Secondary Endpoint #2, Confirmed Progressive Disease (cPD) will be defined as initial disease progression determined through independent review (a.k.a. unconfirmed PD), AND also either (i) a new lesion or (ii) any one of the following criteria (modified iRANO criteria):

- A further 25% increase or greater in the sum of bi-perpendicular diameters of enhancing tumor, occurring at least 4 weeks after the initial event of PD/PsPD;
- Significant increase in T2/FLAIR non-enhancing lesion attributable to tumor growth;
- Death (all deaths are counted as events).

A secondary analysis will, in addition to the MRI findings, take into account the clinical status of the patient, as follows:

- Non-temporary increase in steroid dose >2 mg/day not associated with the unconfirmed PD event;
- Significant clinical decline not attributable to other causes;

15.4. DEFINITION OF TUMOR RESPONSE

Resection of GBM typically focuses on removing the enhancing tissue as that is supposed to be the area of active tumor growth. Incomplete resections result in residual enhancing disease post-surgery and most patients also have non-enhancing disease areas surrounding the enhancing lesion. Tumor response will use pre- and post-randomization measurements of enhancing and non-enhancing disease. Modified RANO criteria will be applied allowing for evaluation of non-measurable disease to determine response rates.

[5] Radbruch et al. 2010: Neuro Oncol. 2011 Dec 6.

15.5. TIME TO TUMOR PROGRESSION

Time to tumor progression is assessed from nadir tumor burden (post operative or Baseline) to the date of the first observation of objective disease progression measured by MRI and confirmed if necessary by scans as described above in section 14.2.

Patients who have not progressed by the end of the study will continue to be followed for tumor progression or tumor recurrence, for survival (Section 14.5) and for their medical history.

15.6. SAFETY

Toxicity is monitored and graded according to NCI Common Terminology Criteria for Adverse Events (Appendix F). The overall incidence of AE is compared between the treatment cohort and the placebo cohort.

15.7. SURVIVAL TIME

Survival calculated from randomization to death, due to any cause.

Patients enrolled in the study will be followed for survival. If a patient has progressed to the primary end point and was living at last follow-up, the site will contact the patient, as scheduled (see below and Appendices A-C) to ascertain survival status.

Patients who are presumed alive, and who have not returned to the study site for a scheduled visit, will be contacted by the study site at the patient's pre-study contact telephone number to ascertain patient status. These contacts will be attempted weekly for 4 weeks. If no information is obtained as to patient status, a certified letter will be sent to the last known patient address. If no response is returned, then secondary or tertiary contact numbers will be utilized. The telephone numbers of patient locaters will be obtained with the patient's permission at the time of enrollment in the study. Patient locators will be identified by the patient as persons who would be aware of change of address, phone number, employment and/or school. The patient locator will be contacted to ascertain the location and/or status of the enrolled patient. In the event that information cannot be obtained from locator contacts, patient status, as alive or dead, will be tracked. The follow-up of subjects for survival and medical history extends until death regardless of the duration of study medication treatment or follow-up for the primary endpoint.

15.8. KARNOFSKY PERFORMANCE STATUS

Patients are graded according to KPS. The performance status over time is compared between patients receiving DCVax-L or placebo.

16. STATISTICAL CONSIDERATIONS

The full statistical considerations underlying the endpoints and intended analyses are described in the Statistical Analysis Plan, which is provided as Appendix H to this protocol. A summary overview is provided below.

This statistical analysis plan (SAP) is intended to serve as the roadmap for evaluating data (Trial Data) acquired in the Phase III clinical trial of Northwest Biotherapeutics, Inc. (NWBT) DCVax®-L autologous dendritic cells (DCs) pulsed with tumor lysate antigen, as adjuvant therapy to standard primary treatments in patients with newly diagnosed and recurrent glioblastoma multiforme (GBM), Protocol No. 020221, v7.0 (the Protocol or the Trial).

This SAP has been jointly developed by three independent biomedical/clinical trial statistical experts. The SAP describes our method for analysing the Trial Data and the impact of DCVax®-L on the course of disease as accurately as possible with endpoints as described below, in accordance with scientific developments that have emerged since inception of the trial.

The original Protocol primary endpoint was to compare progression-free survival (PFS) of the trial treatment arm with a placebo cohort. The original Protocol secondary endpoint was to compare overall survival (OS) of the trial treatment arm with the placebo cohort. However, two major real-world developments took place during the course of the Trial:

- Scientific appreciation of the phenomenon of pseudo-progression advanced, highlighting the virtual impossibility of distinguishing radiation-induced oedema, and vaccine-induced immune-cell infiltration and/or inflammation, from true disease progression. Until a broadly accepted definition of this distinction is settled, the subjectivity of its determination suggests that the trial data should be studied in reference to a more objectively ascertained Trial endpoint than PFS, which is OS (below); and

- Such a large percentage of patients made use of the crossover option in the Protocol that the original control arm became substantially depleted and insufficient for OS analyses within the Trial. When the Trial began in 2007, per the demand of investigators and patients it was necessary to include a crossover option in the Protocol in order to recruit and retain patients. This crossover option allowed patients from both the DCVax®-L arm and the control arm of the Trial to receive DCVax®-L treatment following progression (recurrence), while they and all other parties (including the Sponsor and investigators) remained blinded as to what treatment they received before crossover. Approximately 90% of all patients in the Trial made use of this crossover, resulting in the substantial depletion of the control arm.

These two key developments require corresponding adaptation of the methodology for evaluating the data, specifically:

(a) designating survival (OS) as the trial's primary endpoint and first secondary endpoint--as survival is the patients' ultimate goal--while also retaining the original progression-free survival (PFS) criteria as an additional secondary endpoint, to the extent PFS may ultimately be ascertained from analysis of the Trial Data; and

(b) replacement of the Protocol placebo control cohort with a large, closely matched, independently chosen external control group—in each case as described below:

- Endpoints: The SAP (Section 1.2) adopts the following endpoints as a basis for demonstrating efficacy:

  - ***Primary Endpoint: OS*** relative to external controls.
  - ***First Secondary Endpoint: OS following recurrence***, relative to external controls; and
  - ***Additional Secondary Endpoints***: To the extent demonstrably ascertainable from analysis of the Trial Data, confirmed PFS, and original Protocol endpoints PFS and OS.

- External Controls: Depletion of the Protocol placebo cohort is addressed in this SAP by comparing primary and secondary endpoint results in the Trial treatment arm with external control cohorts, consistent with the FDA's December 2019 Draft Guidance

on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.

The identification of appropriate external controls was done through a systematic literature search which has been conducted by the independent expert firm, York Health Economics Consortium, UK. This independent expert analysis was checked and confirmed with a panel of independent neuro-oncology experts who were not involved in the Trial. In addition, the statistical analysis includes methodologies to ensure matching of these identified external controls to the DCVax®-L trial population based on known prognostic factors, applied by independent statisticians.

REDACTED (SUPERSEDED BY SAP)

17. INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study patients. The PI must assume that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.
All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each patient signs a form indicating their consent to participate prior to receiving any study-related procedures (see Appendices D and E).

17.1. COMPETENT AUTHORITIES/INSTITUTIONAL REVIEW BOARD/ETHICS BOARD

This protocol and relevant substantive data must be submitted to the appropriate CA/IRB/IEC for review and approval before the study can be initiated. Amendments to the protocol are also submitted to the CA/IRB/IEC prior to implementation of any change. The Sponsor must receive a letter that documents CA/IRB/IEC approval prior to initiation of study. The PI or designee is responsible for informing the CA/IRB/IEC of the progress of the study and for obtaining annual CA/IRB/IEC renewal. When the study is completed the CA/IRB/IEC must be informed; the PI or designee should provide the CA/IRB/IEC with a summary of the results of the study. The PI or designee must notify the CA/IRB/IEC, in writing, of any SAE (see Section 11.2).

18. ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

18.1. PRE-STUDY DOCUMENTATION

The following documentation required by the FDA must be received by the Sponsor, or its designee, prior to initiation of the trial: FDA Form 1572; curricula vitae of the PI and all Sub-Investigators; signed Protocol Agreement; copy of the correspondence from the IRB/EC indicating approval of the protocol and Informed Consent Forms, signed by the IRB/EC chairperson or designee; an IRB/EC membership list containing the names and occupations of the IRB/EC members; copy of the Informed Consent Forms that were reviewed and approved by the IRB/EC.

18.2. STUDY SITE TRAINING

Before initiation of the study, the Sponsor, or its designated representatives will review and discuss the following items with the Investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE

reporting, Good Clinical Practice guidelines, CRF/eCRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. Additional documents with instructions for study compliance and CRF/eCRF completion will be provided.

18.3. DOCUMENTATION

The documentation of clinical data needs to be stored by the Sponsor according to legal requirements. The PI and study staff has responsibility for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the Sponsor, the FDA, and/or other applicable regulatory agencies/competent authorities at any time, and should consist of the following elements: patient files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the Competent Authorities, IRB/EC, site, and Sponsor); and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

18.4. ACCESS TO SOURCE DATA

The PI will permit the Sponsor's representatives to monitor the study as frequently as the Sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. The CRF/eCRF and related source documents will be reviewed in detail by the Sponsor’s representative at each site visit. Only original source documents are acceptable for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the CRF/eCRF, such as past history, secondary diagnoses, and concomitant medications. Other study records, such as correspondence with the Sponsor and the Competent Authorities, and IRB/EC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of the FDA or other regulatory agencies.

18.5. DATA COLLECTION

Electronic case report forms must be completed and submitted for each patient enrolled in the study. Any changes or corrections made to the CRF/eCRF must be subsequently reviewed and signed by the PI. All data fields in the CRF/eCRF must be completed to avoid queries.

18.6. PROTOCOL INTERPRETATION AND COMPLIANCE

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB/EC and relevant Competent Authorities approval. The Sponsor is responsible for submitting protocol amendments to the FDA as described in 21 CFR § 312.30 (Protocol Amendments) and other regulatory agencies according to national, state or local requirements. The Sponsor, or its designee, is always available to answer protocol- or patient-related questions.

18.7. STUDY MONITORING AND DATA COLLECTION

A representative from the Sponsor will visit the study center periodically to monitor adherence to the protocol, applicable FDA regulations and/or other regulatory agencies national, state or local requirements, and the maintenance of adequate and

accurate clinical records. Electronic case report forms are reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The Sponsor or its designee is permitted to access patient medical records, laboratory data and other source documentation as needed to appropriately monitor the trial.

18.8. DISCLOSURE OF DATA/PUBLICATION

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by the FDA or other regulatory agencies, the Sponsor or its designee and by the IRB/EC.

The Study is designed as a multicenter study and not powered for analysis and presentation of Study results by individual Study sites. It is anticipated that the final results of this study will be submitted to a peer-reviewed scientific journal. Authorship on such a paper will be acknowledged with customary scientific practice. As such, without the expressed permission of the Sponsor, only clinical Study data relating the Study as a whole will be published. If permission is granted by Sponsor for publication of ancillary data from individual sites, prior to submission for publication of any manuscript or presentation of any poster, presentation, abstract or other written or oral material that describes the results of Study, Institution and/or PI shall provide Sponsor at least 60 days (or as otherwise specified in the sites executed Clinical Trial Agreement) to review any such materials. Such materials shall not divulge any of Sponsor's Confidential Information, and Institution and/or PI shall promptly remove any Confidential Information as requested by Sponsor. If requested by Sponsor, the PI and Institution shall delay the submission of any publication or presentation up to 60 days from the date of Sponsor's request for such a delay. In addition, Sponsor has the right to require that any publication or presentation concerning the Study will acknowledge Sponsor's support.

18.9. ETHICAL CONSIDERATIONS

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

18.10. INFORMED CONSENT

The PI assumes the responsibility of obtaining written Informed Consent for each patient or the patient's legally authorized representative before any study-specific procedures are performed.

Patients meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible patients the opportunity to participate in the study. Patients or parents/legal guardians of all candidate patients will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part

of obtaining a proper Informed Consent. Patients will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The Sponsor or designee will review the informed consent prior to submission to the IRB/EC. The form is to be signed and dated by the patient or patient's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the patient's medical records, and copy maintained with the patient's study records. The date and time of time of the
Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the patient participation schedule in scope or activity, or increases the potential risk to the patient, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the Sponsor or designee and approved by the IRB/EC prior to use. The revised Informed Consent Form must be used to obtain re-consent from any patients currently enrolled in the study if the patient is affected by the amendment, and must be used to document consent from any new patients enrolled after the approval date of the amendment.

18.11. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval. A photocopy of the IRB/EC notification of approval must be forwarded to the Sponsor or its designee before any investigational supplies will be shipped to the PI.

The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior Sponsor and IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Copies of all study-related correspondence between the Investigator and the IRB/EC must be provided to the Sponsor, or its designee, by the Investigator. The PI or designee must promptly notify the IRB/EC of any SAE occurring at the site and of any safety reports (e.g., IND Safety Reports) received from the Sponsor, or its designee, and must copy the Sponsor, or its designee on that correspondence.

The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of patient risk involved in the study, but not less than once per year and at the completion or termination of the study.

18.12. PATIENT PRIVACY

The Sponsor and the Investigator affirm and uphold the principle of the patient's right to privacy. The Sponsor, it's designates and the Investigator shall comply with applicable national and local privacy laws.

To verify compliance with this protocol, the Sponsor, or its designee, will require that the Investigator permit the Sponsor, or its designee's monitor to review the patient's original medical records. Should access to such medical records require a waiver or authorization separate from the statement of Informed Consent, the Investigator will obtain such permission in writing from the patient before the patient is entered into the study.

19. STOPPING THE STUDY

The Sponsor may decide to stop the study at any point, for any reason.
The following reasons will lead to premature termination of the trial:

- New convincing information leading to unfavorable risk-benefit assessment of DCVax-L, including occurrence of significant toxicity associated with DCVax-L;
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons;
- Discontinuation of development of DCVax-L.

APPENDIX A: SCHEDULE OF EVENTS

Visit	1	2	3	4		5		6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
	Surgery	Post-surgery MRI	Pre-leukapheresis	Leukapheresis	Radiation and Chemotherapy	Baseline Visit [b]	Enrollment	**Immunizations**																				End of Treatment	Survival Follow-up
								1	**2**	**3**	**4**	**5**		**6**		**7**			**8**			**9**			**10**				
						-1 wk		**Time 0[d]**	**day 10**	**day 20**	**2 Mo**	**4 Mo**	**6 Mo**	**8 Mo**	**10 Mo**	**12 Mo**	**14 Mo**	**16 Mo**	**18 Mo**	**20 Mo**	**22 Mo**	**24 Mo**	**26 Mo**	**28 Mo**	**30 Mo**	**32 Mo**	**34 Mo**	**36 Mo**	**On-going**
Temozolomide (Stupp Protocol)[a]																													
Consent to collect tumor	**X**																												
Collection of tumor	**X[m]**																												
Consent to Study			**X**																										
History	**X[e]**		**X**																										
Enrollment & Randomization							**X**																						
Physical Exam [p]						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Neurological Exam						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Vital Signs[n]						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
KPS						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
MRI of brain[r]	**X**	**X[e]**				**X**					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
CBC and Differential			**X**			**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Blood Chemistry[f]			**X**			**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Urinalysis			**X**																									**X**	
Pregnancy test			**X**			**X**																							
anti-DNA[g]						**X**		**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Virology Testing[h]			**X**																										
Leukapheresis[o]				**X**																									
Blood for Immune Monitoring[ik]								**X**		**X**		**X**		**X**		**X**			**X**			**X**			**X**				
Injection of Study Drug[j]								**X**	**X**	**X**	**X**	**X**		**X**		**X**			**X**			**X**			**X**				
AE Assessment			**X**	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Survival[lq]																													**X**

Visit Windows for Schedule of Events:

Baseline Visit: two weeks (± 2 days) after completion of chemo-radiation
Time 0: target ≤7 days after Baseline
Days 10 and 20, month 2: ± 2 days
Months 4, 8, 12, 18, 24, 30: ± 1 week, but >6 weeks between immunizations
All visits, including immunization dates, are calculated from day 0 (the date of the first immunization), and for the purposes of this protocol, a 28-day month is used for calculating visits.

Footnotes to Schedule of Events A

[a)] See Appendix B for treatment guidelines. Administration of adjuvant temozolomide is minimally modified from the guidelines to allow for vaccine dose window adherence.

[b)] Tests done at the baseline visit complete Screening examinations. The patient must meet all eligibility criteria verified at screening to be enrolled in the study.

[c)] Limited history to assess potential study eligibility, including age, absence of prior malignancies including other brain cancers, no bilateral disease, no known HIV-1,2, HTLV 1,2, or Hepatitis B,C infection, no conflicting prior treatments.

[d)] Time 0, the day of the first injection, takes place approximately 1 week after the baseline visit (Visit 5).

[e)] MRI done typically 1-3 days after surgery

[f)] Comprehensive metabolic panel, including electrolyte balance, and hepatic and renal functions.

[g)] Anti-DNA antibodies are measured as markers of induced autoimmunity. Results from this test are not required prior to immunizations.

[h)] Virology testing is performed prior to leukapheresis.

[i)] Ten (10) 10mL Green-Top tubes of whole blood plus one Red-Top tube are drawn at Time 0. Subsequent blood draws for immune monitoring are drawn prior to injection and require ten 10mL Green-Top tubes plus one Red-Top tube. After the blood draw, the tubes are shipped to the contract laboratory for development of immune monitoring tests.

[j)] A sufficient amount of DCVax-L or autologous MNC is shipped to the site for a minimum of 5 and up to 10 i.d injection visits (2 injections for each visit). Some patients may not receive 10 immunizations due to insufficient material, in which case they will receive placebo without this information being conveyed to the physician or the patient. Due to interference with immune function, it is strongly recommended that adrenal steroids not be used during the 21-day time window that starts 10 days before and ends 10 days after each DCVax-L immunization. If steroid therapy is clinically indicated, doses should be kept as low as possible (e.g. 2 mg qd).

[k)] Blood for immune monitoring may only be drawn and shipped M-Th. Immune monitoring sample shipments will NOT be received on Saturdays. Please schedule these visits accordingly: Time 0, Day 20, 4 Month, 8 Month, 12 Month, 18 Month, 24 Month, 30 Month. A window of -2 days is allowable to accommodate Friday shipping restrictions. Samples should be drawn pre-injection.

[l)] Survival follow-up will be conducted through quarterly phone calls and may involve public record searches conducted by Omnitrace.

[m)] If MGMT methylation status is not tested as SOC, slides for determination of MGMT methylation status should be sent to the central lab. Refer to the study manual for information on collecting MGMT methylation status.

[n)] Vital signs including heat rate, respiration rate, and blood pressure should be collected pre-injection and every 30 ± 5 minutes for 2 hours post injection. Pre-injection vitals should be recorded in the CRF/eCRF.

[o)] The standard operating procedures, policies, and guidelines utilized by the apheresis center may supersede the suggested guidelines outlined in this protocol. A patient may have a repeat leukapheresis procedure if the initial harvest did not generate enough cells to create study drug. Steroids should be stopped or must be tapered to lowest clinically acceptable dose (i.e. no more than 4 mg qd) approximately 7 days prior to leukapheresis.

[p)] Physical exam includes height (baseline only) and weight.

[q)] Includes GBM related health and medical status.

[r)] Optional tumor burden tests using other imaging modalities (per local regulations) may be performed and submitted for central review, but are unlikely to influence the outcome of MRI review.

APPENDIX A1: SCHEDULE OF EVENTS - OPTIONAL CROSSOVER ARM

Crossover Visit		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	
		Immunizations																				End of Treatment	Survival Follow-up
		1	2	3	4	5		6		7			8			9			10				
		Time 0	day 10	day 20	2 Mo	4 Mo	6 Mo	8 Mo	10 Mo	12 Mo	14 Mo	16 Mo	18 Mo	20 Mo	22 Mo	24 Mo	26 Mo	28 Mo	30 Mo	32 Mo	34 Mo	36 Mo	On-going
Physical Exam [a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
KPS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MRI of brain					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC and Differential[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[be]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[e]		X																				X	
Serum/Urine Pregnancy Test[e]		X																					
anti-DNA[de]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection of DCVax®-L		X	X	X	X	X		X		X			X			X			X				
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival[fh]																							X

Visit Windows for Schedule of Events:

Baseline Visit: two weeks (± 2 days) after completion of chemo-radiation
Time 0: target ≤7 days after Baseline
Days 10 and 20, month 2: ± 2 days
Months 4, 8, 12, 18, 24, 30: ± 1 week, but >6 weeks between immunizations
All visits, including immunization dates, are calculated from day 0 (the date of the first immunization), and for the purposes of this protocol, a 28-day month is used for calculating visits.

Footnotes to Schedule of Events- A1 Optional Crossover (Open Label) Arm

[a)] Physical exam includes weight.

[b)] Comprehensive metabolic panel, including electrolyte balance, and hepatic and renal functions.

[c)] Urine Pregnancy Test results will be required prior to the first crossover dose. Serum pregnancy test will be drawn but results not required prior to immunization.

[d)] Anti-DNA antibodies are measured as markers of induced autoimmunity.

[e)] Results from this test are not required prior to the first immunization.

[f)] Survival follow-up will be conducted through quarterly phone calls.

[g)] Vital signs including heat rate, respiration rate, and blood pressure should be collected every 30 ± 5 minutes for 2 hours post injection.

[h)] Includes GBM related health and medical status.

APPENDIX B: DETAILED TIMELINE FOR POST RADIATION PERIOD

Day	Week	Treatment
-21	-3	Last day of radiation therapy
-7	-1	MRI
-6		
-5		
-4		*≥4 days rest*
-3		
-2		
-1		
0	0	Immunization #1
1		*≥9 days rest*
2		
3		
4		
5		
6		
7	1	
8		
9		
10		Immunization #2
11		*≥9 days rest*
12		
13		
14	2	
15		
16		
17		
18		
19		
20		Immunization #3
21	3	*≥7 days rest*
22		
23		
24		
25		
26		
27		
28	4	
29		
30		
31		1st temozolomide cycle
32		
33		
34		
35	5	
36		

APPENDIX C

APPENDIX C: GUIDELINE FOR TEMOZOLOMIDE USAGE

DETAILED TEMOZOLOMIDE USAGE GUIDELINES

Per the dosing guidelines on the temozolomide website and the Stupp article (Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma).

All patients:
With Radiation - 75 mg/m² daily, 7 days per week from the first to the last day of radiotherapy, 42 days, but for no longer than 49 days.

Adjuvant (Post Radiation) - Patients receive six or more cycles of adjuvant temozolomide according to the standard 5-day schedule every 28 days. For the first cycle the dose is 150 mg/m² daily and increased to 200 mg/m² daily beginning with the second cycle if no toxic effects.

Dose modifications for toxicity:
With Radiation - No dose reductions are recommended, however, dose interruptions may occur based on patient tolerance. The temozolomide dose can be continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x10^9/L, common toxicity criteria (CTC) non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 1.** PCP prophylaxis is required during the concomitant administration of temozolomide and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade ≤ 1).

Table 1. Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption[a]	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 and <100 x 10^9/L	<10 x 10^9/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count ≥ 1.5 x 10^9/L; platelet count ≥100 x 10^9/L; CTC non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting).
TMZ = temozolomide; CTC = Common Toxicity Criteria.

Adjuvant (Post Radiation) – Approximately Four weeks after the first DCVax-L immunization, temozolomide is administered for an additional 6 or more cycles of maintenance treatment. Dosage

in Cycle 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m², if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of temozolomide should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to **Tables 2** and **3**.

Table 2. Temozolomide Dose Levels for Maintenance Treatment

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

Table 3. Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

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

a: TMZ dose levels are listed in **Table 2**
b: TMZ is to be discontinued if dose reduction to <100 mg/m² is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.
TMZ = temozolomide; CTC = Common Toxicity Criteria.

APPENDIX D

APPENDIX D: PERFORMANCE STATUS SCALES

KARNOFSKY PERFORMANCE SCALE[1]

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

References:

1. Karnofsky, DA: Meaningful clinical classification of therapeutic responses to anti-cancer drugs. Clin Pharmacol Ther 1961;2:709-712.
2. Stanley, KE: Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 1980;65:25-32.

APPENDIX E

APPENDIX E: MODIFIED GRADING OF INJECTION SITE REACTION TOXICITY

The following toxicity grading is for vaccine injection site reactions (dermatology/skin). It is quantitative, objective, more consistent, and works well for reporting skin site reaction as an AE:

Grade 0 None

Grade 1 Erythema and induration of treatment site of ≤2 cm of surrounding tissue accompanied by small ulceration.

Grade 2 Erythema and induration of treatment sites >2 to <4 cm of surrounding tissue and/or some surrounding rash; accompanied by large ulceration >2 to <4 cm.

Grade 3 Extensive (e.g., dermal sloughing) regional ulceration of ≥4 cm at each injection site.

Grade 4 Diffuse rash requiring hospitalization, I.V. support, and parenteral medication.

APPENDIX F

APPENDIX F: NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 3.0

Found at: http://ctep.cancer.gov/forms/CTCAEv3.pdf

APPENDIX G: CONTRACTORS AND CONSULTANTS

Several contractors will be involved in the conduct and monitoring of this clinical trial. Specific procedures involving these contractors are provided in the study manual.

- Parexel International, a contract research organization, will assist the Sponsor in performing the Sponsor responsibilities in the EU (site selection, clinical monitoring, pharmacovigilance, submissions to the ethics committees, and clinical data management) noted in the regulations. SynteractHCR, Inc., a contract research organization, will assist the Sponsor in performing the Sponsor responsibilities in the U.S. (site selection, clinical monitoring, pharmacovigilance, regulatory submissions, and clinical data management) noted in the regulations.
- Dr. Vijay Hingorani, M.D., Ph.D. will serve as the Medical Monitor through Specialty Pharma Consulting, Inc.
- A consulting statistician will perform statistical analyses for the Data Monitoring Committee (DMC).
- ICON Medical Imaging, an imaging core laboratory, will evaluate radiographic scans to determine patient eligibility, response, and tumor progression for all study sites.
- Quest Diagnostics will perform central pathology review for protocol eligibility on original tumor specimen slides for all study sites.
- ACM Global will collect, store, and analyze protocol directed laboratory samples for study sites.
- Cognate Bioservices will provide manufacturing and QC services in the US. Cognate has recently relocated from Sunnyvale, CA to Memphis, TN.
- Fraunhofer-Institut für Zelltherapie und Immunologie IZI will provide manufacturing and QC services in the EU. Fraunhofer is located in Leipzig, Germany.
- Immunologic Monitoring and Cellular Products Laboratory will receive and process the immune monitoring samples collected in the USA.
- The Rayne Institute at King's College London, or a to be determined equivalent vendor, will provide processing and storage of immune monitoring samples in the EU.
- Omnitrace or an equivalent vendor will conduct public record searches to determine or confirm vital status/date of death for all patients
- Q^2 Solutions, Mayo Labs, or an equivalent vendor will conduct the analyses towards

APPENDIX H: STATISTICAL ANALYSIS PLAN

The SAP is attached as a separate document

A Phase II Clinical Trial Evaluating DCVax®-Brain, Autologous Dendritic Cells Pulsed with Tumor Lysate Antigen for the Treatment of Glioblastoma Multiforme

Version 4.0
10.22.07

Study Agent: DCVax-Brain (Autologous Dendritic cells and GBM tumor lysate)
Protocol Number: 020221
IND Number: 10206

Sponsor: **Northwest Biotherapeutics, Inc.**
Address: 18701 120th Avenue NE, Suite 101, Bothell, Washington 98011
Phone: 425-608-3008
Fax: 425-608-3009

Manufacturer: Cognate BioServices, Inc.
Address: 709 E. Evelyn Avenue, Sunnyvale, California 94086
Phone: 408-616-1000
Fax: 408-616-1005

Principal Investigator Agreement:

I the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice, the ethical principals set forth in the Declaration of Helsinki and the U.S. Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Financial Disclosure of interests in Sponsor (21 CFR 54), Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312).

Signature:_____ Date_____

Print name:_____

Protocol Synopsis

Protocol Title: A Phase II clinical trial evaluating DCVax-Brain, autologous dendritic cells (DC) pulsed with tumor lysate antigen for the treatment of Glioblastoma multiforme (GBM)

Protocol No.: 020221, v4.0, 10.2207

Study Agent: DCVax®-Brain (Autologous DC and patient tumor lysate).

Indication: Treatment of patients with newly diagnosed GBM.

Objectives:
Primary: The primary objective of this study is to compare progression-free-survival (PFS) between patients in the treatment cohort and patients in the placebo cohort.

Secondary: The secondary objective is to compare overall survival (OS) between patients in the treatment cohort (DCVax-Brain) and patients in the placebo cohort. Other secondary outcomes include time to progression of disease, time to decline in physical functioning, survival at 6, 12, 18, 24, 36 and 48 months, safety, and evaluation of immune responses induced by DCVax-Brain.

Study Design:
The study is designed as a randomized, placebo-controlled, double blinded, multi-center Phase II clinical trial. The trial will enroll approximately 240 patients with newly diagnosed GBM into the investigational arm, of which approximately 160 patients will be randomized into the treatment cohort and will receive DCVax-Brain as adjuvant therapy to standard treatment and approximately 80 patients will be randomized into the placebo cohort and will receive standard treatment supplemented with autologous PBMC (placebo). An additional, separate informational arm will be composed of patients who display progressive GBM at completion of radiation/chemo-therapy, or who are otherwise determined to be ineligible for the investigational arm of the study after leukapheresis.

Patients in the treatment cohort will receive up to 10 immunizations with DCVax-Brain over a period of 3 years. Patients in the placebo cohort will receive up to 10 immunizations with autologous PBMC over a period of 3 years. Patients in the informational arm will receive up to 10 immunizations with DCVax-Brain over a period of 3 years.

Patients in the placebo cohort who progress during the study will be offered a crossover option to receive DCVax-Brain after progression has been independently verified.

Safety of DCVax-Brain will be assessed by comparing the frequency and intensity of adverse events, along with physical examination data and clinical laboratory testing results during the study period, between DCVax-Brain treated patients and controls.

Population:
Patients, 18 to 70 years old with newly diagnosed GBM (Grade 4 astrocytoma), who have undergone surgery are eligible to enroll in the protocol. Patients enrolled in the protocol who have received external beam radiation therapy with concurrent Temodar® chemotherapy according to the Stupp protocol (Stupp et al., N Engl J Med 352: 987-96, 2005), with no evidence of disease progression following radiation therapy, are eligible to be randomized to the treatment cohort or placebo cohort of the study, and patients who have progressive disease at that time are eligible for treatment with DCVax-Brain in the informational arm. All patients must have a Karnofsky

Performance Score of ≥70, 8 week life expectancy, no other prior malignancy within the last 10 years, and no active infections.

Treatment Schedule:
Two intradermal (i.d.) injections of DCVax-Brain or autologous PBMC (placebo) per treatment; each injection consisting of 1.25 million DC in 0.15 ml, in the upper arm. Treatments will be given at days 0, 10, 20, and at months 2, 4, 8, 12, 18, 24 and 30.

Assessments:
Disease progression is assessed every 2 months by brain MRI scans, according to the imaging parameters in the imaging manual. KPS is assessed every 2 months during clinic visits.

Primary and Secondary Endpoint, Hypothesis, and Analytic Method
Primary Endpoint- Progression free survival (PFS): Time to objective demonstration of disease progression or death.

Hypothesis: Survival free of disease progression will be longer for patients treated with DCVax-Brain in the treatment cohort than for patients treated with autologous PBMC in the placebo cohort.

Analytic Method: Proportional hazards (Cox) regression.

Secondary Endpoint- Overall survival.

Hypothesis: Survival will be longer for patients treated with DCVax-Brain in the treatment cohort than for patients treated with autologous PBMC in the placebo cohort.

Analytic Method: Cox regression.

Northwest Biotherapeutics, Inc.

DCVax®-Brain

Protocol 020221, Version 4.0

A PHASE II CLINICAL TRIAL EVALUATING DCVax-BRAIN, AUTOLOGOUS DENDRITIC CELLS PULSED WITH TUMOR LYSATE ANTIGEN FOR THE TREATMENT OF GLIOBLASTOMA MULTIFORME

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1. GENERAL INFORMATION

1.1. PROTOCOL TITLE

A Phase II Clinical Trial Evaluating DCVax®-Brain, Autologous Dendritic Cells (DC) Pulsed with Tumor Lysate Antigen for the Treatment of Glioblastoma Multiforme (GBM)

1.2. SPONSOR INFORMATION

Northwest Biotherapeutics, Inc.
18701 120th Avenue NE, Suite 101
Bothell, WA 98011

1.3. PERSONS AUTHORIZED TO SIGN PROTOCOL AMENDMENTS

Alton Boynton, Ph.D., President and Chief Executive Officer, Northwest Biotherapeutics, Inc. (NWBT)
Marnix Bosch, M.B.A., Ph.D., Chief Technical Officer, NWBT

1.4. INVESTIGATOR INFORMATION

A list of investigators and sites participating in this study is on file at NWBT.

1.5. CONSULTANTS AND CONTRACTORS FOR THE STUDY

Several contractors will be involved in the conduct and monitoring of this clinical trial. Specific procedures involving these contractors are provided in the study manual.

- Synteract, Inc., a contract research organization, will assist the sponsor in performing the sponsor responsibilities (site selection, clinical monitoring, pharmacovigilance, regulatory submissions, and clinical data management) noted in the regulations.
- A consulting statistician will perform statistical analyses for the Data Monitoring Committee (DMC).
- RadPharm, Inc., an imaging core lab, will evaluate radiographic scans to determine patient eligibility, response, and tumor progression.
- Bernd W. Scheithauer, M.D., through Mayo Clinical Trial Services, will perform central pathology review for protocol eligibility on original tumor specimen slides.
- Mayo Clinical Trial Services will collect, store, and analyze protocol directed laboratory samples.

2. INTRODUCTION TO THE PROTOCOL

2.1. INTRODUCTION

DCVax-Brain was used in a Phase I/II clinical trial to immunize patients with GBM (Grade 4 astrocytoma), following primary therapy that consisted of surgery, followed by conventional external beam radiation and Temodar® (temozolomide) chemotherapy during radiation and for six cycles after radiation. No serious adverse events (SAE) attributable to the study drug were observed. Based on promising data in patients with GBM indicating slowing of disease progression and increased survival, the following Phase II study, which is designed as a pivotal study, will be conducted in patients presenting with newly diagnosed GBM.

2.2. PHASE I/II CLINICAL TRIAL

The results of the Phase I/II trial to test the safety of DCVax-Brain are described below. There is an abundance of cancer literature supporting the safety and potential efficacy of using autologous DC pulsed with autologous tumor lysate antigen, in which 11 trials and 129 patients are described, with no evidence of serious toxicities or autoimmunity (see investigator's brochure for a complete listing of references). This literature includes an article by Yu et al. (Yu, JS et al, Cancer Res 64:497-9, 2004) in which 14 patients with malignant glioma treated with tumor lysate-pulsed autologous DC are described. The reported data show an absence of SAE related to the treatment and the induction of immune responses and suggest clinical benefit.

The Phase II protocol is predicated on a Phase I/II trial (BB-IND #11053) carried out by Dr. Linda Liau at the University of California, Los Angeles (UCLA). In this trial, 12 patients with newly diagnosed GBM were immunized with three injections of autologous DC that were pulsed with 100 µg of autologous tumor cell lysate antigen. Three patients received 1 million DC per immunization, four patients received 5 million DC per immunization, and five patients received 10 million DC per immunization. Table I shows the demographics of patients with newly diagnosed GBM that were enrolled in the Phase I/II clinical trial.

Table I. Demographics of Patients in the Phase I/II Clinical Trial: (BB-IND #11053)

Patient Subject Number	Age	Gender	Diagnosis	On-Study Date
1	39	Male	GBM	7/07/03
2	40	Male	GBM	9/24/03
3	34	Male	GBM	10/29/03
4	40	Female	GBM	2/04/04
5	26	Male	GBM	3/10/04
6	70	Female	GBM	9/22/04
7	49	Male	GBM	11/10/04
8	59	Male	GBM	12/01/04
9	64	Male	GBM	4/29/05
10	66	Male	GBM	7/12/05
11	43	Male	GBM	4/12/06
12	45	Female	GBM	4/19/06
13	58	Male	GBM	5/8/06

2.2.1. Safety

The immunizations with tumor lysate antigen-pulsed autologous DC were well tolerated. There were no SAE related to the treatment. The most frequently observed adverse events (AE) are injection site reactions, fatigue, and low-grade fever.

2.2.2. Clinical Follow-Up

Thirteen patients with newly diagnosed GBM have been enrolled to date (Table II below; data as of September 10, 2007). Ten patients have surpassed the historical median time to progression (TTP) of 6.9 months, without evidence of disease progression. Overall, six patients (#1, #4, #7, #9, #10 and #136) have progressed and two patients (#6, #12) were lost to follow up before progression could be unequivocally established; the patients with no progression of disease have follow-up times ranging from 20.7 to 57.8 months from surgery. Six patients (#1, #4, #6, #7, #9, #13) have died, and the remaining 7 patients are alive with survival times (from initial surgery) ranging from 21 to 57.8 months. Historically, at the same institution (UCLA), patients similar to those enrolled in the trial (R.P.A. classes III and IV) have median times to disease progression of 8.1 months (± 7.3 months), and median survival times of 17 months (± 13.9 months). In a multicenter trial, 287 patients treated post surgery with radiotherapy plus concomitant Temodar achieved median progression free survival (PFS) of 6.9 months from surgery (95% confidence interval, 5.8 to 8.2) and median survival of 14.6 months from surgery (95% confidence interval, 13.3 to 16.8; Stupp et. al., New England J. Med. 352: 987-96; 2005). In the Phase II trial, PFS and survival times will be calculated from time of enrollment, which is expected to occur approximately three months after initial surgery.

Table II. Summary of Tumor Progression and Survival Data in the Phase I/II Trial (BB-IND # 11053)

Subject Number	DC Dose x 10^6	Total Time to Progression (months)	Survival (months to Sept. 10, 2007)	Survival Status (Sept 10, 2007)
1	1	13.1	33.8	Dead
2	1	No progression to date	>50.7	Alive
3	1	No progression to date	>53.1	Alive
4	5	9.2	18.0	Dead
5	5	No progression to date	>57.8	Alive
6	10	Lost to follow-up @13.1	23.1	Dead
7	10	13.9	36.4	Dead
8	10	No progression to date	>37.0	Alive
9	10	5.7	13.6	Died
10	10	26.4	>30.1	Alive
11	5	No progression to date	>20.7	Alive
12	5	Lost to follow-up @7.6	>21.0	Alive
13	1	8.0	10.3	Dead

2.2.3. Immunological Follow -Up

Immune monitoring of patients is in progress. Sections from the resected tumors are stained for the expression of known tumor-associated antigens, including gp100, Trp-2, Her-2 and viral antigens such as CMV. If tumor sections stained positive for such antigens, the patients' peripheral blood mononuclear cells (PBMC) were assessed for expansion of CD8+ T-cells specific for the antigens using tetramer staining. Because of limited availability of reagents, these experiments were carried out only for those patients that express the MHC haplotype HLA-A2*01.

Table III. Summary of Immune Responses in the Phase I/II Trial (BB-IND #11053)

Patient Number	DC Dose (# cells/injection)	HLA type	Tetramer analysis
1	1 x 10^6	A03, A68	Not done
2	**1 x 10^6**	**A201, A68**	**↑ anti-gp100, Trp-2**
3	**1 x 10^6**	**A201**	**↑anti-CMV, gp-100, Trp-2**
4	**5 x 10^6**	**A201, A11**	**-**
5	5 x 10^6	A0404, A03, DR4, DR17	Not done
6	**10 x 10^6**	**A201, A01, DR17, DR11**	**↑ Her2**
7	10 x 10^6	A29, A69, DR7, DR15	Not done
8	**10 x 10^6**	**A201, A63, DR4, DR13**	**↑ gp-100, Trp-2, Her2**
9	10 x 10^6	Not done	Not done
10	**10 x 10^6**	**A201, DRB1**	**↑ Gp-100, Trp-2, Her-2**

These data suggest that DCVax-Brain can induce an immune response against the tumor cell lysate antigens used to pulse the DC.

2.2.4. Summary

DCVax-Brain was used to immunize patients with GBM, following standard primary therapy that consisted of surgery, followed by conventional external beam radiation and Temodar (temozolomide) chemotherapy. No SAE related to the study drug were observed. Typical time to tumor progression from surgery for such patients, if they had not received DCVax-Brain is 8.1 months, and median survival is approximately 17 months. Kaplan Meyer estimates of the median TTP and median survival time for patients treated with DCVax-Brain are 18.1 and 33.8 months respectively. Two patients, with no evidence of progression and survival times (to date) of 40.4, and 42.8 months respectively, mounted strong immune responses to tumor-associated antigens present in their tumor tissue. These data, if reproducible in a larger study, would demonstrate that patients with GBM can derive significant clinical benefit from treatment with DCVax-Brain.

3. OVERVIEW OF DCVAX-BRAIN PHASE II CLINICAL TRIAL

This protocol describes a randomized, placebo-controlled, double blinded, multi-center, Phase II clinical trial for DCVax-Brain in patients with newly diagnosed GBM. The primary endpoint for the study is PFS. The study is powered such that if the primary endpoint is met, as specified in the statistical considerations section of this protocol, the company intends to request accelerated approval for DCVax-Brain. In addition, the study is powered to detect meaningful clinical benefit for the first secondary endpoint, overall survival (OS), which is also the confirmatory clinical endpoint for the study. Other secondary endpoints include TTP, decline in Karnofsky Performance Status (KPS), landmark analyses of survival, and immune responses to DCVax-Brain.

The underlying hypothesis is that DCVax-Brain, i.e. DC generated from the peripheral blood of a patient with GBM and pulsed (combined) with tumor lysate antigen, will safely (1) delay time to disease progression, (2) increase survival and (3) induce anti-tumor immunity when administered as a series of intradermal (i.d.) injections in newly diagnosed patients. DCVax-Brain is intended as adjuvant therapy to standard primary treatments, which include surgical resection, conventional external beam radiation therapy with concurrent Temodar chemotherapy, followed by additional cycles of Temodar chemotherapy essentially following the protocol according to Stupp et al. (N Engl J Med 352: 987-96, 2005; “The Stupp Protocol”).

3.1. OBJECTIVES

3.1.1. Primary objective

The primary objective of this study is to compare PFS between patients in the treatment cohort and patients in the placebo cohort.

3.1.2. Secondary objectives

- to compare OS, measured as time-to-death between patients treated with DCVax-Brain in the treatment cohort and patients treated with autologous PBMC in the placebo cohort;
- to compare time to progression of disease (TTP; includes as events all radiographic evidence of disease progression; all deaths are censored) between patients treated with DCVax-Brain in the treatment cohort and patients treated with autologous PBMC in the placebo cohort;
- to compare survival at 6, 12, 18, 24, 36 and 48 months between patients treated with DCVax-Brain in the treatment cohort and patients treated with autologous PBMC in the placebo cohort.

3.1.3. Tertiary objectives

- to compare immune responses between patients in the treatment cohort and patients in the placebo cohort:
- to compare decline in physical functioning, measured by KPS evaluation, between patients in the treatment cohort and patients in the placebo cohort.

3.1.4. Safety objective

- to evaluate further the safety of DCVax-Brain.

3.2. STUDY POPULATION

Patients with newly diagnosed GBM are eligible for this protocol. Diagnosis of GBM will be confirmed through independent central pathology review. Patients must have a surgically accessible tumor for which surgical resection, with intent to perform a gross total or near gross total resection, is indicated.

3.3. STUDY DESIGN

The study is designed as a randomized, placebo-controlled, double blinded, multi-center Phase II clinical trial, with a crossover option for patients in the placebo group who have progressed. The trial will enroll approximately 240 patients with newly diagnosed GBM into the investigational arm of the study, of which approximately 160 patients will be randomized to the treatment cohort and 80 will be randomized to the placebo-cohort. Additional patients, consisting of those who have progressive disease following radiation, will form an informational arm and will receive DCVax-Brain. At minimum, all patients will receive standard treatment consisting of: a) surgical resection, b) external beam radiation with concurrent chemotherapy (Temodar), and followed by additional 28-day cycles of Temodar chemotherapy (see Appendix C for details).

Patients enrolled in the protocol who have received external beam radiation therapy with concurrent Temodar chemotherapy according to the Stupp protocol (Stupp et al., N Engl J Med 352: 987-96, 2005), with no evidence of disease progression following radiation therapy, are eligible to be randomized into the investigational arm of the study, and patients who have progressive disease or are otherwise ineligible for the investigational arm are eligible to receive treatment with DCVax-Brain in the informational arm. The number of patients to be enrolled in the informational arm will be determined as events transpire during the trial.

The study schedule anticipates an approximate active enrollment period of 9 months. An initial efficacy analysis for the primary endpoint (PFS) will be performed after 110 events (progression or death) have occurred in the treated patients and the placebo controls combined, which is expected to occur approximately 5 months after enrollment of the last patient.

All patients will be followed for the collection of data on late progression and survival until death. The analysis for the survival endpoint will be done after 72 deaths have occurred in the treatment cohort and placebo cohort combined, which we expect to occur approximately 9 months after completion of enrollment. Schematics of the study timeline are presented in Appendix A, and a detailed overview of the timeline following radiation therapy is provided in Appendix B.

All patients receive up to 10 immunizations of DCVax-Brain (treatment cohort and informational arm) or autologous PBMC (placebo cohort) at days 0, 10, 20, and at months 2, 4, 8, 12, 18, 24 and 30) following recovery from surgery and radiation with concurrent Temodar chemotherapy.

For each immunization, patients will receive two intradermal injections (i.d.) of approximately 150µl (0.15mL) containing 1.25 million cells each (DCVax-Brain or

PBMC) in an outpatient setting. Patients are observed for acute toxicity for 2 hours post-injection.

3.4. ESTIMATED ACCRUAL

It is estimated that accrual will average two participants in the investigational arm and less than one participant in the informational arm per month per site, at approximately 40 clinical sites participating in the study. The total accrual is to be approximately 240 patients in the investigational arm, and an unknown number of patients in the informational arm of the study.

3.5. NAME OF SPONSOR/FUNDING SOURCE

Northwest Biotherapeutics, Inc. (NWBT), Bothell, Washington.

4. SAFETY CONSIDERATIONS

The major component of DCVax-Brain is autologous DC loaded with autologous tumor lysate antigen. DC are generated by *ex vivo* culturing of adherent peripheral blood monocytes with the cytokines granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-4 (IL-4) for 5-7 days. DC are harvested, loaded with tumor lysate antigen, washed extensively, and cryopreserved as DCVax-Brain. After washing, only trace amounts of GM-CSF, IL-4, and unloaded antigenic material are introduced into the patient. For each immunization, two vials containing DCVax-Brain are thawed and two injections of approximately 150µl each are given i.d.

Autologous PBMC are purified directly from a leukapheresis through density gradient centrifugation, and contain no foreign substances other than the diluent and cryopreservative.

The Phase II clinical trial is predicated on a Phase I/II clinical trial carried out at UCLA (BB-IND #11053). No Grade 3 or 4 toxicities related to the treatment were observed in this trial, leading to the preliminary conclusion that DCVax-Brain is safe to administer to patients with brain cancer.

There are a number of published studies referring to similar therapies that have utilized *ex vivo* manipulated autologous DC pulsed with autologous tumor lysate. No serious toxicities or clinically meaningful evidence of autoimmunity were observed in 11 trials comprising a total of 129 patients (fully referenced in accompanying Investigator's Brochure).

5. PATIENT ELIGIBILITY

5.1. INCLUSION CRITERIA

All patients, unless specified otherwise below, must meet the following inclusion criteria at the indicated time points.

<u>Determined at pre-screening</u>

Subjects ≥18 and ≤70 years of age at surgery who are capable of informed consent. Patients must be able to understand and sign the informed consent (template forms are provided in Appendices D and E) indicating that they are aware of the investigational nature of this study.

- Patients must have a life expectancy of >8 weeks.

<u>Determined at or around surgery, and prior to pre-leukapheresis</u>

- Primary therapy must consist of surgical resection with the intent for a gross or near total resection of the contrast-enhancing tumor mass, followed by conventional external beam radiation therapy and concurrent Temodar chemotherapy. Patients having a biopsy only will be excluded.
- Patients with newly diagnosed, unilateral GBM (Grade IV) are eligible for this protocol. An independent central neuropathologist will review this diagnosis during the enrollment process.
- All Patients must have sufficient tumor lysate protein that was generated from the surgically obtained tumor material. This determination will be made by Cognate BioServices, Inc. (Cognate) and communicated to the clinical site through the Sponsor, or its designee.

Determined at pre-leukapheresis

- Patients must have adequate bone marrow function (e.g., hemoglobin >10 g/dl, white blood count 3600-11,000mm^3, absolute granulocyte count ≥1,500/mm^3, absolute lymphocyte count ≥1,000/mm^3, and platelet count ≥100K/mm^3. Eligibility level of hemoglobin can be reached by transfusion. These values are determined by a central laboratory (Mayo Central Labs).
- Adequate liver function (SGPT, SGOT, and alkaline phosphatase ≤4.0 times upper limits of normals (ULN) and total bilirubin ≤1.5mg/dl), and adequate renal function (BUN or creatinine ≤1.5 times ULN) prior to starting therapy. These values are determined by a central laboratory (Mayo Central Labs).

Determined at baseline

- Patients must have a KPS rating of ≥70 at the Baseline Visit (Visit 5) (refer to Appendix F, Performance Status Scales).
- Patients may have received steroid therapy as part of their primary treatment. Steroid treatment must be stopped at least 10 days prior to the first immunization with DCVax-Brain.
- Patients in the investigational arm of the study must be willing to forego cytotoxic anti-tumor therapies except Temodar while being treated with DCVax-Brain. DCVax-Brain and placebo must be given as described and Temodar must be given essentially according to the Stupp Protocol (see Appendices B and C for Temodar schedules and detailed treatment guidelines).

5.2. EXCLUSION CRITERIA

Patients may not be enrolled in the trial if they have any of the following exclusion criteria, at the indicated time points:

Determined at pre-screening

- History of prior malignancy except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer or other cancers that were deemed fully resolved 10 or more years prior to Visit 1 of the study.
- History of immunodeficiency or autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, scleroderma,

polymyositis-dermatomyositis, juvenile onset insulin dependent diabetes, or vasculitis.

- Inability to obtain informed consent because of psychiatric or complicating medical problems.
- Any known genetic cancer-susceptibility syndromes.

Determined at or around surgery

- Bilateral or metastatic disease detected at diagnosis, during surgery or at post-surgical magnetic resonance imaging (MRI). Tumors may cross into, but not beyond the corpus callosum.
- Post operative MRI scan evidence of biopsy only without significant tumor resection.
- Implantation of Gliadel® wafers at surgery.

Determined at pre-leukapheresis

- Positive HIV-1, HIV-2, HTLV-1, hepatitis B surface antigen, or hepatitis C antibody.
- Subjects with organ allografts.
- Allergies to reagents used in this study.
- Inability or unwillingness to return for required visits and follow-up exams.
- Any previous cytotoxic drug therapies, excluding corticosteroids and temozolomide concurrent with radiation therapy.

Determined at baseline

- Patients in the investigational arm of the study may not have radiographic evidence of disease progression at baseline, compared to the post surgery MRI. This will be verified by independent radiology review during the enrollment process.
- Patients may not be taking medications that might affect immune function: The following are exceptions: nonprescription strength doses of NSAIDS, acetaminophen or aspirin. A list of such medications will be provided to investigators and updated as required.

Safety considerations, determined at baseline: the following exclusion criteria preclude patients from being enrolled in any arm of the study:

- Acute infection: any active viral, bacterial, or fungal infection that requires specific therapy. Antibiotic therapy must be completed at least 7 days prior to the first immunization.
- Active uncontrolled infection. Examples are a sexually transmitted disease (STD), herpes, uncontrolled tuberculosis, malaria, etc.
- Fever ≥101.5^{o}F. If considered possibly transient, retesting is allowed.

- Unstable or severe intercurrent medical conditions such as unstable angina, uncontrolled arythmias, Crohn's Disease, ulcerative colitis etc.
- Females of child-bearing potential who are pregnant or lactating or who are not using adequate contraception (surgical, hormonal or double barrier, i.e. condom and diaphragm).

6. TREATMENT PLAN

6.1. TREATMENT PLAN OVERVIEW

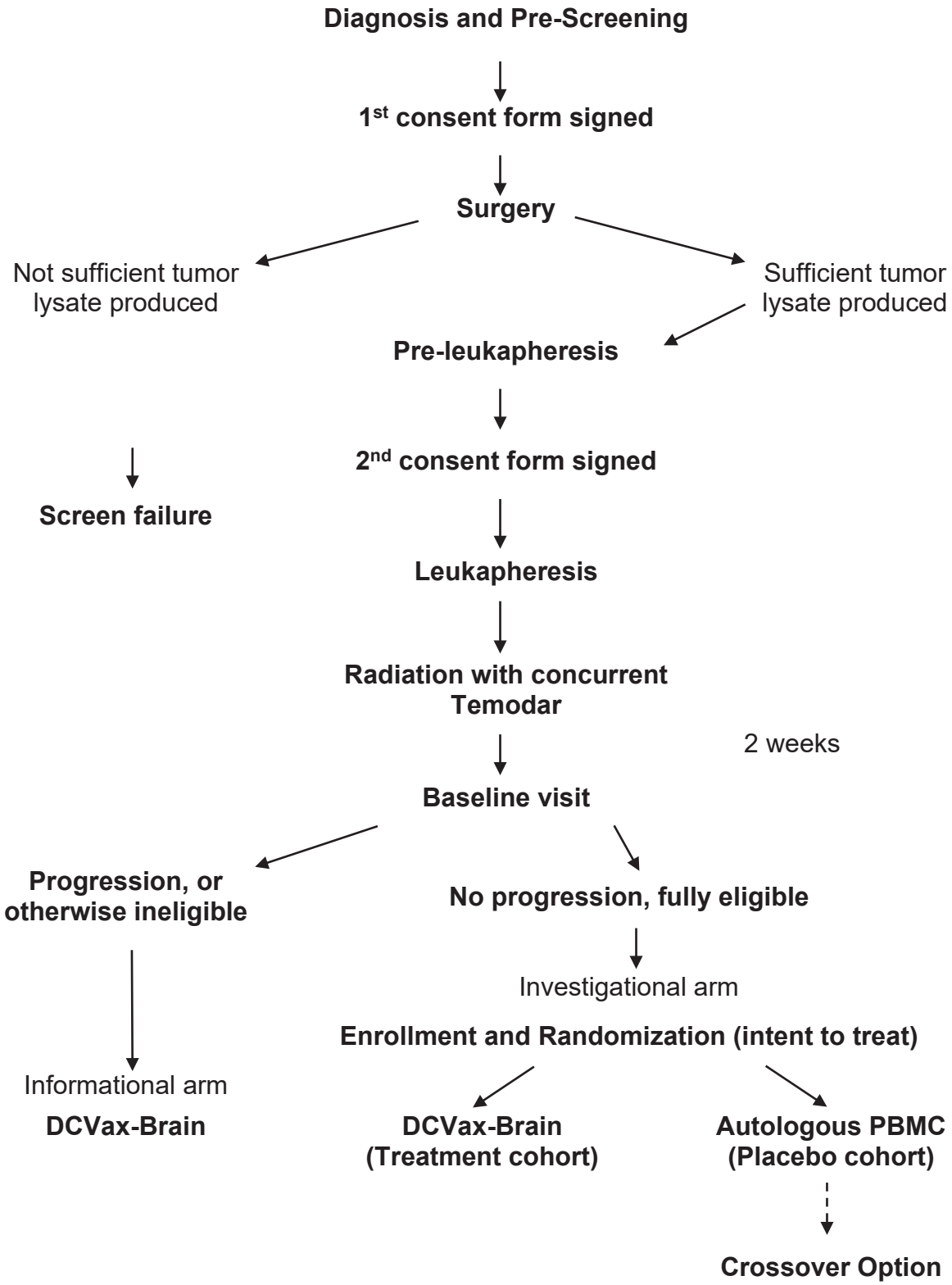
After the informed consent for the collection of the tumor has been signed (Appendix D), all subjects will undergo surgery at a center participating in the trial. As much as possible, or approximately 2-5 grams of the tumor material obtained from surgical resection will be placed in a sterile container containing a mixture of tissue-dissociating enzymes. This is the source for the tumor lysate material that is used as antigen in this study. The container is shipped to Cognate, Sunnyvale, California for manufacturing of the tumor lysate antigen preparation.

Following recovery from surgery, patients for whom it has been established that sufficient tumor lysate was generated undergo a pre-leukapheresis visit to determine viral status and bone marrow function. Patients with negative viral status and adequate bone marrow function proceed to leukapheresis to harvest the DC precursors, prior to initiation of external beam radiation therapy with concurrent chemotherapy. Peripheral blood mononuclear cells (PBMC) are purified from the leukapheresis material at Cognate, and an aliquot of the PBMC is cryopreserved for use as placebo for patients who are randomized to the placebo cohort. The remainder of the PBMC is used to prepare DCVax-Brain. Both DCVax-Brain and the placebo are tested at Cognate prior to release to the study site. Patients for whom sufficient tumor lysate was not generated are not eligible to continue on this protocol.

All subjects who had a leukapheresis will undergo conventional external beam radiation therapy and concurrent Temodar chemotherapy as part of standard primary treatment, initiated as soon as possible, typically 1-3 weeks after surgery (Appendices A & B).

Two weeks after completion of radiation and concurrent chemotherapy treatment, subjects will undergo the Baseline Visit, during which the final tests to determine eligibility for the investigational arm of the protocol are performed. Patients with progressive disease at the Baseline Visit (as determined by MRI) are assigned to the informational arm; eligible patients who do not have progressive disease at the Baseline Visit are enrolled in the investigational arm of the study (intent to treat), and are randomized to receive DCVax-Brain in the treatment cohort or autologous PBMC in the placebo cohort. Randomization and treatment assignment takes place approximately 1 week after the Baseline Visit. At the baseline visit, patients must be scheduled to return to the clinic 1 week after the Baseline Visit to receive their first immunization. The study drug, containing 2.5 million DC per immunization (two injections of 1.25 million DC each per immunization, 150 μl each), is injected i.d. (not subcutaneously) into a clean area of the upper arm.

Table IV. Treatment Schedule Overview
(Detailed authoritative schedule provided in Appendices A and B).



6.2. SCREENING PROCESS

Pre-Screening: The following parameters should be established prior to entering the screening process: age (must be in range), absence of prior malignancies (within the last 10 years) and no known HIV-1,2 infection or known pregnancy. If these conditions are satisfied, patients are entered into the screening process.

Visits 1-3 (see Appendix A) are used to screen patients for eligibility for the trial. The following tests and assays determine eligibility:

Visit 1 (Surgery): All patients must have newly diagnosed, unilateral GBM without metastases. All pathologic diagnosis of GBM will be reviewed by independent pathology review.

All patients will sign an informed consent form (Appendix D) to allow collection of the tumor and perform study activities required for screening.

Collection of tumor tissue: approximately 2-5 grams of tumor tissue needed to maintain eligibility.

Visit 2 (Post-surgery MRI): MRI scans pre- and post-surgery need to document extent of resection against enrollment criteria. Patients must have a surgically accessible tumor for which surgical resection, with intent to perform a gross total or near gross total resection, is indicated. Biopsy only does not satisfy eligibility rules. MRI scan (post-surgical) must demonstrate that a significant resection was performed. All MRI scans will be reviewed by independent radiology review.

The post-surgery MRI will be used to quantitatively determine the extent of resection for purposes of the statistical analyses in section 13.2.3 and 13.3.3. Extent of resection will be defined as the amount of residual tumor volume measured in mm^3.

The amount of tumor lysate protein is determined as soon as possible after surgery by Cognate. Determination that sufficient tumor lysate protein was generated is required for a patient to remain eligible and to undergo leukapheresis.

Visit 3 (Pre-leukapheresis): Just prior to proceeding to leukapheresis, patients for whom it has been determined that sufficient tumor lysate protein was generated, and for whom the diagnosis of GBM is independently confirmed in central review, patients are assessed for viral status and bone marrow and liver function. The following tests are done at the pre-leukapheresis visit:

- Hematology: CBC, differential, platelets.
- Virology testing: HIV-1, 2, HTLV-1, Hepatitis B, C.
- Serum Chemistries: calcium, SGOT, SGPT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, electrolytes, magnesium and glucose.
- Urinalysis: normal routine urinalysis.

The second consent form is also signed at this visit.

Visit 4 (Leukapheresis): Patients proceed to leukapheresis as soon as they are sufficiently recovered from surgery, the second consent form is signed and after

continued eligibility has been determined (sufficient tumor lysate generated, negative viral status, adequate bone marrow and liver function).

Visit 5 (Baseline): Visit 5 takes place 2 weeks (± 2 days) after the last day of radiation therapy with concurrent Temodar chemotherapy. At the Baseline Visit, the patient undergoes an MRI to assess disease progression and blood draws to assess eligibility.

Patients who have evidence of objective disease progression (measured by MRI, compared with post-surgery MRI and verified by independent review), or who are otherwise ineligible at this time will be enrolled in the informational arm of this study. Patients who do not have progressive disease at baseline are enrolled in the investigational arm of the study, and will be randomized to receive DCVax-Brain or placebo at a 2:1 ratio. All remaining inclusion and exclusion criteria must be met for all patients to be enrolled in the investigational arm.

In the event that the scan and or clinical signs cannot unambiguously determine progression or stability (inflammatory artifact, necrosis, other post operative/ radiation changes) then perfusion MRI, MRI-spect, PET, or Thallium-spect scans can be performed at institutional preference. If tumor status is still equivocal, the patient is not eligible for enrollment into the investigational arm, but can be enrolled into the informational arm. The decision whether progression has occurred at this point is made through central review.

The following tests and examinations are to be performed at Baseline (Visit 5):

- MRI with and without contrast of the brain to confirm absence of disease progression (verified by independent radiology review).
- History and Physical Examination.
- KPS.
- Neurological Exam.
- Pregnancy test: Serum hCG pregnancy test is performed on female subjects of child bearing potential.
- Anti-DNA antibodies as a marker of autoimmune disease.
- Optional tumor burden tests: Positron Emission Tomography (PET) scan and/or Magnetic Resonance (MR) spectroscopy scan and/or Thallium-SPECT may be performed at the investigator's discretion, or if necessary to determine if recurrence has occurred.

Eligibility to be enrolled in the investigational arm of the study will be determined on the basis of the outcome of these tests, which are to be performed within the shortest possible time after the Baseline Visit (target <1 week) to ensure earliest administration of DCVax-Brain.

6.3. INVESTIGATIONAL ARM: ENROLLMENT AND RANDOMIZATION

In order for a patient to be enrolled in the investigational arm of the study. they must meet all eligibility criteria above, including absence of disease progression following radiation with concurrent Temodar chemotherapy, confirmed by central independent review of the post radiation MRI performed at the Baseline Visit (Visit 5) compared to the post-surgery MRI;

The patients meeting these criteria are enrolled in the investigational arm, and immediately randomized into the treatment cohort or the placebo cohort of the study (enrollment and randomization happen concurrently). Final review prior to enrolling and randomizing a patient into the investigational arm of the trial will be made by the Sponsor and the outcome will be communicated to the clinical site via facsimile.

The patients who have sufficient tumor lysate, have undergone a leukapheresis, and who have progressive disease after completion of radiation (as determined by central review) will be enrolled in the informational arm of the study.

6.4. OPTIONAL CROSSOVER ARM

Patients enrolled in the investigational arm for whom disease progression is established at any point in time after randomization (as defined in section 12.1 of this protocol, and verified by independent review) will be unblinded as to their cohort assignment (treatment vs. placebo). Patients that were in the placebo cohort will be given the option to receive DCVax-Brain, or any other established or experimental treatment of the physician's choice.

6.5. BRIEF DESCRIPTION OF MANUFACTURING PROCESS FOR DCVAX-BRAIN

REDACTED

6.6. BRIEF DESCRIPTION OF MANUFACTURING PROCESS FOR PLACEBO

REDACTED

6.7. ADMINISTRATION OF DCVAX-BRAIN OR PLACEBO

Over the course of the study patients will receive up to 10 DCVax-Brain or placebo injections at days 0, 10, 20, and at months 2, 4, 8, 12, 18, 24 and 30.

For injections at days 0, 10, 20 and at month 2, the variance may be ±2 days but the minimum interval between injections must be at least 9 days. Thereafter, the variance can be ±1 week with a minimum interval of 6 weeks between injections.

At the clinical site, two vials of DCVax-Brain or placebo are thawed at room temperature for each immunization. No more than 1 hour should elapse between thawing and administration. For each immunization, two separate i.d. injections of approximately 0.15 mL (150 ul) each are given via an insulin syringe with minimal dead space to deliver a total of 2.5 million tumor lysate antigen-loaded DC (DCVax-Brain) or autologous PBMC (placebo). Injections are administered in the upper arm (alternating arms at each treatment visits). If subcutaneous injection occurs, this should be recorded on the case report form (CRF), and the injection SHOULD NOT be repeated. The patient is observed for 2 hours after administration of each injection.

7. PATIENT EVALUATION

7.1. ON-STUDY CLINICAL EVALUATIONS

Clinical evaluations take place according to the Schedule of Events (Appendix A). Follow-up visits should be scheduled to occur once every two months, ±2 weeks. The window between these visits should be as close to 2 months as possible, no

less than 6 weeks, and no more than 3 months. The following tests and procedures are completed, although not all tests may be done at each visit; see the detailed study timeline in Appendix A.

- Physical Examination
- KPS
- Neurological Exam
- MRI of brain with and without contrast every 2 months ±2 weeks, with a minimum of 6 weeks between scans
- Optional tumor burden tests: PET scan and/or MR spectroscopy scan and/or Thallium-SPECT scans may be performed at the investigator's discretion, if necessary as part of standard care or if necessary to confirm tumor progression as indicated by MRI
- Hematology: CBC, differential, platelets
- Serum Chemistries: including calcium, magnesium, SGOT, SGPT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, electrolytes, and glucose
- Serum markers of Autoimmune disease (anti-DNA)

7.2. IMMUNOLOGICAL STUDIES

The immunological studies that are intended for this clinical trial are initially exploratory in nature. Future expansion of these studies to determine immunological correlates for clinical efficacy may be undertaken based on initial results.

For patients in the investigational arm, blood will be obtained and PBMC harvested and stored for future analysis. The following tests for monitoring the immune response to DCVax-Brain may be used for this study. Refer to Appendix A for the timing of these blood draws.

- Mixed lymphocyte-DCVax-Brain culture
- Cytokine release (e.g. through Elispot)
- Immunohistochemical staining of resected brain tissue
- Feasibility

Some of the above assays (mixed lymphocyte-tumor cell cultures, cytokine release) are dependent on the availability of DCVax-Brain material in excess of what is required for treatment. Excess material will not be available for all patients and it may not be available for any patients. Assays will therefore be limited based on the amount of available material.

8. TOXICITY MONITORING

Both acute and chronic toxicities are recorded and reported to the Sponsor, or its designee, and will be reviewed by the DMC at scheduled meetings. Monitoring for acute toxicity takes place during and immediately following injection for a period of 2 hours at the study site. Patients are observed for the development of an immediate localized allergic reaction or anaphylactic reaction during this time. Chronic toxicity is evaluated at the bi-monthly physical examination and by scheduled clinical laboratory tests.

9. PATIENT DISCONTINUATION OF ACTIVE TREATMENT

An explanation for discontinuing treatment is recorded for each patient discontinuing treatment on the appropriate CRF. The Sponsor, or its designee, must be notified immediately if a patient discontinues treatment. All patients, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- if the sponsor decides to stop the study;
- at Investigator's discretion;
- at the patient's request;
- if the patient enrolls in a trial of another investigational agent for the treatment of GBM;
- Grade 4 or life-threatening toxicity (See Section 11, Adverse Events) attributable to DCVax-Brain;
- injection site reactions of Grade 3 or higher, according to the grading in Appendix G, Modified Grading of Injection Site Reaction Toxicity;
- development of clinical signs and symptoms of autoimmune disease;
- pregnancy;
- development of an allergic reaction of Grade 2 or higher, with exception of transient (<1 hour) fever or other constitutional symptoms, localized urticaria, and transient (<30 seconds) shortness of breath, or immunological reaction Grade 3 or higher to DCVax-Brain, with the exception of low grade fever of <39°C which resolves spontaneously or with antipyretics within 48 hours.

n.b. patients in the treatment cohort who have progressed may elect to continue receiving DCVax-Brain immunizations, in addition to physician's choice of therapy.

10. CONCOMITANT MEDICATIONS

Medications taken by the patients in each of the arms of the study, starting at the Baseline Visit and continuing throughout the study are recorded on the appropriate CRF. Limitations on use of concomitant medications are listed below:

- Patients may take small amounts of topical or inhaled corticosteroids, as well as corticosteroids used as replacement therapy for adrenal steroids, e.g., <0.75 mg of Decadron, or equivalent.
- Therapeutic doses of adrenal steroids may not be used by patients in the investigational arm of the study during the 20-day time window that starts 10 days before and ends 10 days after each DCVax-Brain immunization.
- Patients may take doses of nonprescription strength NSAIDS, acetaminophen, ibuprofen or aspirin for non-chronic headache, muscle pain, trauma or prophylaxis as long the dosing regimens comply with the recommended dose in the product labeling.
- Patients may receive antihistamine therapy for colds or allergies at non-prescription doses, but patients in the treatment arm should not take these medications within 5 days before or after an immunotherapy injection.
- Patients may take vitamin supplements within a dose range not associated with toxicity.
- Patients may take cimetidine or other H_2 blockers.

- Other medications that may affect immune function are not allowed for patients in the treatment arm of the study. A list of such agents is provided to the sites.
- The use of other investigational agents is not permitted for patients in the investigational arm of the study.
- Active immunotherapy is not allowed for any patient in any arm of the study.
- Temodar: Temodar administration is essentially per the Stupp Protocol schedule for control patients and is minimally modified from the Stupp protocol schedule for treated patients to avoid interference with DCVax-Brain immunizations. See Appendices B and C for details.

11. ADVERSE EVENTS

11.1. ADVERSE EVENT RECORDING

An AE is defined as development of any change in signs or symptoms or abnormal lab results at any time after signing the consent form for the study, and may include a single symptom or sign, a set of related symptoms or signs, or a disease while receiving the study drug. All AE must be recorded (even if a causal relationship to the study drug is unlikely) and reported on the CRF.

Patients are instructed to report any AE to the investigator. On each day of evaluation, the patient is questioned regarding any new medical problems and new or changed medications. All AE are documented in the source document and on the AE Form (located in the CRF).

The intensity of all AE not localized to the injection site of the study drug is graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTC) version 3.0 (Appendix I). AE that are considered by the investigator to be localized or related to the injection site shall be graded according to Modified Grading of Injection Site Reaction Toxicity (Appendix G).

The relationship of an AE to study treatment is characterized as “not related”, “unlikely related”, “possibly related”, “probably related”, or “definitely related” and is determined by the Study Center physician/Principal Investigator (PI) according to the following guidelines:

- **Not Related**: The adverse event is clearly not related to the study drug and is clearly related to an underlying disease, environmental or toxic factors, or other drug/therapy.
- **Unlikely to be Related**: The adverse event does not follow a reasonable temporal sequence after study drug administration (e.g., too soon or too long after study drug or study drug was not taken) and is plausibly related to an underlying disease, environmental or toxic factors, or other drug/therapy. Events assessed “not likely” related will be considered unrelated to study drug.
- **Possibly Related**: The adverse event occurred in a reasonable time after study drug administration but could be related to an underlying disease, environmental or toxic factors, or other drug/therapy. There is a reasonable possibility of a causal relationship between the study drug and the adverse event.

- **Probably Related**: The adverse event occurred in a reasonable time after study drug administration and is unlikely to be related to an underlying disease, environmental or toxic factors, or other drug/therapy. The event may respond to stopping the study drug.
- **Definitely Related**: The adverse event occurred in a reasonable time after study drug administration but could not be explained by an underlying disease, environmental or toxic factors, or other drug/therapy. The event should respond to stopping the study drug.

11.2. SERIOUS ADVERSE EVENT REPORTING

An SAE is defined as one of the following:

- death;
- an event that is life threatening;
- an event that results in persistent or significant disability/incapacity;
- an event that requires inpatient hospitalization or prolongs hospitalization;
- an event that is a congenital anomaly/birth defect;
- an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

It is anticipated that progressive disease will occur and symptoms from this may well constitute an SAE.

11.3. RECORDING AND FOLLOW-UP OF ADVERSE AND SERIOUS ADVERSE EVENTS

All AE that occur (or that worsen from Baseline status) from leukapheresis through 30 days after the final injection or final study visit will be recorded. Adverse events that occur after enrollment but before immunization will be considered not related to study drug. Duration, severity, and outcome for each AE will be recorded on the CRF Adverse Event Form, and treatment administered will be recorded on the Concomitant Medications pages; this information must also be recorded in the source documentation. Adverse events will be followed until resolution, until no further improvement is expected, or until the patient is lost to follow-up, whichever comes first.

- SAE will be recorded on the Serious Adverse Event Worksheet (provided in the regulatory binder), which will be faxed to the Sponsor, or its designee, indicated in the study manual within 24 hours of becoming aware of the event. A corresponding AE must be recorded in the source documents and the CRF.
- All SAE must be followed until the event has resolved, until no further improvement is expected, or until the patient has been lost to follow-up, whichever comes first.
- AE beginning more than 30 days after the last treatment, that the investigator considers related to study treatment, will be reported to the Sponsor or its designee, indicated in the study manual at any time such events occur.
- Toxicities that were present at the study start and that worsen during the study should be reported as beginning on the date the event worsened, not the date it began pre-study. Event text may include the word “worsened” or “exacerbated.”

- The severity of each AE must be assessed using the NCI CTC, version 3.0.
- Pregnancies occurring during the study will be followed until resolution (termination or birth)

11.4. EXPEDITED REPORTING OF SAE

All SAE that occur from leukapheresis through 30 days after the last study treatment are immediately reportable to the Sponsor, or its designee, regardless of relationship to study treatment. The sponsor or sponsor's designated contact listed in the study manual should be notified by telephone that an SAE has occurred, and a Serious Adverse Event Report Form must be completed and sent to that contact by facsimile or overnight mail within 24 hours of the event. A narrative from the investigator, outlining the details of the AE, its treatment, and its outcome is to be included on this form. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event should be submitted with a Follow-up Serious Adverse Event Report Form as soon as the information becomes available.

Northwest Biotherapeutics is required by regulatory agencies to report all serious and unexpected AE that are possibly, probably, or definitely related to the use of the study drug in clinical studies in an expedited manner. Therefore, investigators are required to provide timely completion and follow-up of the Serious Adverse Event Worksheets.

In addition to notifying the sponsor's designated contact listed in the study manual of SAE, investigators are required by US regulations as described in *21 CFR §312.66 (Assurance of IRB Review)*, to notify their Institutional Review Board (IRB)/Ethics Committee (EC) promptly of all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that the investigator will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. This means that the investigator will report to the IRB/EC all SAE occurring at the investigator's study site(s). In addition, investigators are also required to report to their IRB/EC all SAE that are immediately reportable to this study (i.e., IND Safety Reports), regardless of when the SAE occurred. In these situations, the sponsor or its designee will provide the necessary information to the investigator to report to their IRB/EC in the form of an IND Safety Report Letter.

12. CRITERIA FOR ENDPOINT EVALUATIONS

12.1. DEFINITION OF PROGRESSION AFTER ENROLLMENT

Progression, calculated from randomization, is defined as one of the following:

- In the case of complete resection during primary therapy: a new measurable tumor at the site of the resected tumor, defined as a mass with a longest diameter equal to or greater than 1 cm in at least one dimension, measured by plain and contrast-enhanced MRI. For any doubtful or non-obvious result, necrosis etc., confirmation by PET, or Thallium-spect, or MRI-spect scans must be performed to determine attribution to tumor growth. If not defined by these studies, treatment may proceed and determinations made at the next scheduled MRI. Continuation of treatment AFTER progression has been detected and

confirmed by independent review is allowed, at the election of the investigator and patient. If active treatment is stopped, the patient will be followed until death.

- In the case of incomplete resection during primary therapy: a 25% increase or greater in the residual tumor if the recurrent portion of the tumor is at least 1 cm or greater in its longest diameter, measured by MRI and confirmed by scans above as attributable to tumor growth;
- If resection is indicated for recurrent disease, while radiographic criteria for progression have not been met: surgical resection, subsequently confirmed as progressive GBM by Pathology at the clinical site and to be confirmed by independent pathology;
- Appearance of any new lesion/site at least 1 cm in at least one dimension or greater measured by MRI and confirmed by scans above;
- Death: all deaths are counted as events of progression for the primary endpoint.

Radiographic evidence of disease progression will be evaluated and corroborated by independent radiology review to determine disease progression for purpose of this trial. Standard operating procedures for MRI will be centrally formulated and distributed to all sites. MRIs to assess disease progression are done every 2 months. Unscheduled MRIs or other testing will be recorded on CRFs. If, during unscheduled procedures, there is evidence of disease progression, it must be confirmed through independent review as described above.

12.2. TIME TO TUMOR PROGRESSION

Time to tumor progression is assessed for patients in the investigational arm from enrollment to the date of the first observation of objective disease progression measured by MRI and confirmed by scans above in section 12.1.

Patients who have not progressed by the end of the study will continue to be followed for tumor progression or tumor recurrence, for survival (Section 12.4) and for their medical history.

12.3. SAFETY

Toxicity is monitored and graded according to NCI Common Terminology Criteria for Adverse Events (Appendix I). The overall incidence of AE is compared between the treatment cohort and the placebo cohort.

12.4. SURVIVAL TIME

Survival calculated from randomization to death, due to any cause.

Patients enrolled in both arms of the study will be followed for survival. If a patient has progressed to the primary end point and was living at last follow-up, the site will contact the patient, as scheduled (see below and Appendices A-C) to ascertain survival status.

Patients who are presumed alive, and who have not returned to the study site for a scheduled visit, will be contacted by the study site at the patient's pre-study contact telephone number to ascertain patient status. These contacts will be attempted weekly for 4 weeks. If no information is obtained as to patient status, a certified letter will be sent to the last known patient address. If no response is returned, then

secondary or tertiary contact numbers will be utilized. The telephone numbers of patient locaters will be obtained with the patient's permission at the time of enrollment in the study. Patient locators will be identified by the patient as persons who would be aware of change of address, phone number, employment and/or school. The patient locator will be contacted to ascertain the location and/or status of the enrolled patient. In the event that information can not be obtained from locator contacts, patient status, as alive or dead, will be tracked. The follow-up of subjects for survival and medical history extends until death regardless of the duration of study medication treatment or follow-up for the primary endpoint.

12.5. KARNOFSKY PERFORMANCE STATUS

Patients are graded according to KPS. The performance status over time is compared between patients on the investigational arm receiving DCVax-Brain or placebo.

13. STATISTICAL CONSIDERATIONS

13.1. STUDY DESIGN

13.1.1. A randomized, placebo controlled, double blind, multicenter, Phase II Clinical Trial, with a crossover option for patients in the placebo cohort who have progressed.

This is a Phase II trial conducted at multiple sites in which subjects with resected GBM receive DCVax-Brain or placebo as adjuvant therapy to standard treatment, including surgical resection, radiation and concurrent chemotherapy (Temodar), followed by post radiation chemotherapy. PBMC are isolated by leukapheresis from the subject in order to culture DC. DCVax-Brain consists of autologous DC pulsed with autologous tumor lysate antigen. Placebo consists of autologous PBMC.

All patients will receive up to 10 immunizations of DCVax-Brain or placebo (at days 0, 10, 20, and at months 2, 4, 8, 12, 18, 24 and 30) following recovery from surgery and radiation and chemotherapy.

13.2. PRIMARY ENDPOINT, HYPOTHESIS, AND ANALYTIC METHOD

13.2.1. Endpoint: Time to objective demonstration of disease progression or death, measured from time of randomization, (PFS)

13.2.2. HYPOTHESIS: PFS, measured form time of randomization, will be longer on average for patients in the investigational arm, who were treated with DCVax-Brain compared to placebo.

13.2.3. ANALYTIC METHOD: Proportional hazards (Cox) regression. The effect of DCVax-Brain will be tested in a model with the treatment group, age, extent of resection, and KPS as covariates, since age, extent of resection (expressed as residual tumor volume after resection), and KPS are considered possibly related to PFS. The effect of treatment should be significant (two-sided p-value for coefficient of treatment group $\leq$ 0.05) to support a conclusion of a significant effect of DCVax-Brain on PFS.

Randomization into the investigational arm of the study takes place after patient eligibility has been confirmed through tests performed at the Baseline Visit.

The analysis will be an intent-to-treat analysis; that is, all randomized patients who contribute any follow-up data for PFS will be included.

13.3. SECONDARY ENDPOINT, HYPOTHESIS, AND ANALYTIC METHOD

13.3.1. ENDPOINT: Time to death (OS)

13.3.2. HYPOTHESIS: Survival, measured from time of randomization, will be longer on average for patients in the investigational arm who were treated with DCVax-Brain compared to placebo.

13.3.3. ANALYTIC METHOD: Cox regression. All randomized patients who contribute any follow-up data for survival will be included in the analysis. The effect of DCVax-Brain will be tested in a model with treatment group, age, extent of resection (expressed as residual tumor volume after resection), and KPS as covariates. The effect of treatment should be significant (two-sided p-value for coefficient of treatment group $\leq$ 0.05) to support a conclusion of a significant effect of DCVax-Brain on OS. Randomization takes place after patient eligibility has been confirmed through tests performed at the Baseline Visit.

The analysis will be an intent-to-treat analysis; that is, all randomized patients who contribute any follow-up data for OS will be included.

13.4. SAMPLE SIZE AND POWER

13.4.1. Primary Endpoint

The primary endpoint will be time to progression of disease or death (PFS). The analysis will be a Cox regression analysis. For the purpose of sample size and power calculations, we assume perfect balance for known prognostic factors between the treatment cohort and the placebo cohort. We also assume median time to disease progression or death from enrollment of 7 and 13.5 months among the placebo cohort and the treatment cohort, respectively. Recent historical data obtained at UCLA demonstrated a median PFS of 5 months for control patients, and 75% of patients had progressed at 7 months. A median PFS for DCVax-Brain treated patients of 13.5 months was assumed for this study for the purpose of calculating power. In the Phase I trial, 70% of patients had PFS >13.5 months. We set the type I error rate (α) at one-sided 0.01, in order to have strong evidence for a beneficial effect of DCVax-Brain. We plan to randomize 240 total patients in a 2:1 ratio (DCVax-Brain:placebo) into the investigational arm: 160 patients in the treatment cohort (DCVax-Brain) and 80 in the placebo cohort (PBMC).

To estimate the power for a comparison of PFS, we use the routine for the log-rank test in PASS 2005 software (Number Cruncher Statistical Systems, Kaysville, Utah). This routine assumes exponential distributions for the endpoint and time to loss to follow-up. Since the log-rank test and Cox regression with treatment group as the only covariate give very similar

results, power for the log-rank test should be a good approximation to the power of the Cox regression analysis. The assumptions of median PFS of 7 and 13.5 months in control and DCVax-Brain-treated patients, respectively, correspond to respective 52-week probabilities of PFS of 0.305 and 0.540. We assume 10% loss to follow-up in both the treatment cohort and placebo cohort in 52 weeks. We plan for an accrual period of 9 months and an additional follow-up period of 5 months, for a total study length for this objective of 14 months, and we assume that 60% of the accrual time will be required for enrollment of 50% of the study patients. Then the power for 240 total patients in the investigational arm, divided at a 2:1 ratio between the treatment cohort and the placebo cohort, is approximately 82%.

We estimate the corresponding number of events required using the formula of Schoenfeld (1983), which gives the total number of events needed, N, as

$$N = (z_\alpha + z_\beta)^2 / [P_1 P_2 (\ln \Delta)^2], \text{ where}$$

z_α and z_β are the points on the standard normal distribution corresponding to type I error rate α and type II error rate (i.e., 1 – power) β, P_1 and P_2 are the proportions of study subjects in the placebo and treatment cohorts, respectively ($P_1 + P_2 = 1$), and Δ is the hazard ratio for placebo compared to treatment subjects (equivalently, inverse of ratio of median times to event). Time to death or disease progression is assumed to follow an exponential distribution. For $\alpha = 0.01$, $\beta = 0.018$, $P_1 = 0.333$, $P_2 = 0.667$, and $\Delta = 13.5/7 = 1.929$, the formula gives a sample size of 110 events, rounded to the next highest integer.

13.4.2. Secondary Endpoint #1

Analysis and assumptions for the secondary objective #1 (OS) will be similar to those described above, with the following changes. The endpoint will be time to death, and the follow-up time is 9 months. For this analysis we assume median times to death of 17 and 34 months among patients in the placebo and treatment cohorts, respectively; these correspond to respective 52 week probabilities of survival of 0.613 and 0.783 and a hazard ratio of 2.0. The type I error rate for this analysis is set at 0.025, one-sided. Then the power of the log-rank test, under assumptions as for the primary endpoint except for median times to death of 17 and 34 months, is approximately 79%. The corresponding number of events, from the Schoenfeld (1983) formula, is approximately 72, rounded to the next highest integer.

13.5. DATA MONITORING COMMITTEE

The sponsor of the study, Northwest Biotherapeutics, is blinded to all patient efficacy data during the trial. Surveillance of emerging study data will be carried out by an independent DMC (see Appendix H for Charter). The DMC will include members with clinical and biostatistical expertise and will be charged with monitoring the quality and integrity of data and the adequacy of recruitment, compliance and follow-up. The DMC will monitor all AE and outcome events, and will identify safety issues of concern. The DMC will meet before the study begins and approximately every 4-6 months thereafter until the end of the trial. Urgent concerns may require one or more

unscheduled meetings in addition to the regularly scheduled meetings. One member of the DMC will be designated as the Medical Contact for the study. The Medical Contact will receive monthly reports from NWBT or designee of all SAE and quarterly reports of all AE, identified by treatment received and including relevant information about each SAE or other AE. The Medical Contact may, at his or her discretion, consult with the DMC chair or other DMC member(s) regarding accumulating AE and/or request the DMC chair to call an emergency meeting of the DMC. Based on its findings at either regularly scheduled or emergency meetings, the DMC may recommend continuing, stopping, or altering the trial.

At its regular meetings, the DMC will review data on recruitment and on both safety and efficacy endpoints. The DMC will see data separated by treatment group. Possible reasons for a recommendation by the DMC to stop the trial are an unacceptable excess of AE among patients treated with DCVax-Brain, an excess of primary endpoint events in the treatment cohort, low power to show a beneficial effect of DCVax-Brain, and insufficient enrollment into the study**.**

13.5.1. Interim analysis

The DMC will conduct one interim analysis to evaluate the conditional power (CP) of the study to show a significant benefit of DCVax-Brain on PFS and OS at the end of the study. The interim analysis will be done approximately one month prior to the projected end of the enrollment period. CP is the power of the study, given the interim results and assumptions on the median time to progression or death and to death in the treated and control groups. CP will be calculated with hazard ratios estimated from the interim data, as well as under the original assumptions of 7 and 13.5 months median time to progression or death and of 17 and 34 months median time to death, and possibly under other assumptions as well. If CP is low for both PFS and OS, then the DMC may recommend stopping the trial for lack of benefit of DCVax-Brain, or increasing the sample size for the trial.

13.6. ADDITIONAL SECONDARY EFFICACY HYPOTHESES, OUTCOME MEASURES AND STATISTICAL METHODS

The following secondary endpoints can provide evidence to support the primary endpoint.

13.6.1. ENDPOINT: Time to progression of disease (includes as events all radiographic evidence of disease progression; all deaths are censored).

HYPOTHESIS: The proportion of patients in the treatment cohort who have disease progression will be lower than the proportion of patients in the placebo cohort who have disease progression.

ANALYTIC METHOD: Cox regression. All enrolled patients will be included in the analysis.

13.6.2. ENDPOINT: Time to decline in KPS.

HYPOTHESIS: Time to decline in KPS will be longer on the average for the treatment cohort patients than for the placebo cohort patients.

ANALYTIC METHOD: Cox regression. All enrolled patients will be included in the analysis.

13.6.3. ENDPOINT: Survival at 6, 12, 18, 24, 36 and 48 months.

HYPOTHESIS: The proportion of patients who are alive at the time of the analysis will be greater in the treatment cohort than in the placebo cohort.

ANALYTIC METHOD: Cox regression with all patients censored past the time point of the analysis. An alternative method will compare the Kaplan Meier probabilities of survival at the times of analysis using a z-test with the estimated survival probabilities and their estimated standard errors.

13.6.4. ENDPOINT: Immunostimulatory response (yes or no). A patient will be considered a responder if one of the following conditions holds at least one time point in the study: a) T cell proliferative response to DCVax-Brain shows a stimulation index of 2 or greater, b) a greater than 3-fold increase in CD8+ cells staining with tumor antigen tetramers.

EVALUATION: immune responses will be compared between patients in the treatment cohort and the placebo cohort.

13.7. SECONDARY ANALYSIS OF COVARIATES

Associations of 1) age, 2) KPS, 3) extent of resection, 4) clinical site, and 5) Temodar® usage with the primary endpoint and first secondary endpoint will be assessed. Proportional hazards regression modeling will be done to determine the sets of covariates independently associated with the endpoints and also to evaluate interactions of these covariates with the effect of treatment with DCVax-Brain. All randomized patients will be included in the analysis.

13.8. OTHER SECONDARY ANALYSES

The primary analysis evaluates time to death or progression of disease, measured from enrollment, for all enrolled patients.

13.8.1. Censored analyses: Secondary analyses will evaluate time to death or progression of disease and censor all patients that have received concomitant medications to treat their brain cancer while enrolled in this study.

13.8.2. From initial diagnosis: Another secondary analysis will compare PFS, OS and TTP, measured from initial diagnosis, between patients in the treatment cohort and placebo cohort.

13.8.3. Effect of crossover: Other secondary analyses will determine the effect of the crossover component of the trial on OS, by a) censoring from the analysis patients who have crossed over from the placebo cohort to DCVax-Brain treatment upon disease progression, and b) comparing OS in a log-rank analysis between patients who have crossed over from the placebo cohort with patients that were in the placebo cohort who have not crossed over.

13.9. SAFETY ANALYSES

During the course of treatment and during the follow-up period, numerous tests are performed at various intervals to monitor toxicity. Laboratory tests include hematology parameters (e.g., hemoglobin level, leukocyte count, platelet count), blood chemistry parameters (e.g., alkaline phosphatase, bilirubin, albumin, SGOT, SGPT, bicarbonate, calcium, glucose, potassium, magnesium, sodium, creatinine), and markers of induced autoimmune disease (e.g., anti-DNA). Physical examination tests monitor vital signs (e.g., blood pressure, temperature) and AE are reported spontaneously (e.g., headache, fatigue, myalgia, tumor pain). All of the above parameters, if they result in AE are graded for toxicity using the Common Terminology Criteria for Adverse Events v.3.0 (Appendix I), 1 to 5 scale.

For the treatment cohort and the placebo cohort, and for each AE, the frequency of subjects experiencing Grades 1, 2, 3, 4 or 5 toxicity will be presented in tabular format and displayed for each assessment. Frequencies of Grade 3 or 4 toxicity in the treatment and placebo cohorts will be compared using a chi-square test. Each SAE, death and discontinuation due to an AE will be described. For the informational arm all AE will be tabulated.

Adverse events will be coded using MedDRA and tabulated by number of patients with each maximum severity (toxicity grade) by system organ class and preferred term. Tables of overall incidence of AE and of AE considered to be related (i.e. possible, probable, or definite) to study treatment will be prepared. Details of all individual patient's AE will be listed.

In addition, since these safety parameters are assessed multiple times on each subject during the longitudinal study, the mean of measurements and CTC toxicity grades, by treatment group, will be graphically displayed and trends over time assessed, e.g., using the Generalized Estimating Equations procedure proposed by Zeger and Liang (Zeger and Liang, Biometrics 42:121-30. 1986).

13.10. OTHER ANALYTIC CONSIDERATIONS

13.10.1. Missing data

When data points, especially in regards to radiographic imaging data, are missing, strong efforts will be made to obtain the missing study information. In spite of these efforts, there will probably be missing data regarding assignment of primary and secondary endpoints.

If a patient misses one or more visits and at the next visit the scan is positive, the event of disease progression will be considered to have occurred midway between the scheduled times of the last non-missing visit and the visit when scan was positive.

A sensitivity analysis will employ one or more of the following three approaches, following directions provided by the DMC:

- Count event as occurring midway between the scheduled times of the last missing visit and the visit when scan was positive.
- Count event as occurring midway between the scheduled times of the last non-missing visit and the first missing visit.
- Count event as occurring at the last scheduled visit which was negative.

13.10.2. Unscheduled visits

Progression of disease may be detected between scheduled visits. In those instances, the actual date when progression is detected will be used to determine TTP. A sensitivity analysis, where TTP is taken as the midpoint between the last visit that was negative, and the next scheduled visit, will also be performed.

13.10.3. Additional Summaries

A summary will be prepared to show dropouts/retention over time in each patient group and for each participating site. The number of missing observations in important variables will be compared between groups.

14. INVESTIGATOR OBLIGATIONS

As indicated on FDA Form 1572, the PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study patients. The PI must assume that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and to all FDA regulations and guidelines regarding clinical trials both during and after study completion.

14.1. INFORMED CONSENT

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each patient signs a form indicating their consent to participate prior to receiving any study-related procedures (see Appendices D and E).

14.2. INSTITUTIONAL REVIEW BOARD

This protocol and relevant substantive data must be submitted to the appropriate IRB for review and approval before the study can be initiated. Amendments to the

protocol are also submitted to the IRB prior to implementation of any change. The Sponsor must receive a letter that documents IRB approval prior to initiation of study. The PI is responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. When the study is completed the IRB must be informed; the PI should provide the IRB with a summary of the results of the study. The PI must notify the IRB, in writing, of any SAE (see Section 11.2).

15. ADMINISTRATIVE CONSIDERATIONS

15.1. PRE-STUDY DOCUMENTATION

The following documentation required by the FDA must be received by the Sponsor, or its designee, prior to initiation of the trial: FDA Form 1572; curricula vitae of the PI and all Sub-investigators; signed Protocol Agreement; copy of the correspondence from the IRB indicating approval of the protocol and consent forms, signed by the IRB chairperson or designee; an IRB membership list containing the names and occupations of the IRB members; copy of the Informed Consent Forms that were reviewed and approved by the IRB.

15.2. STUDY SITE TRAINING

Before initiation of the study, the Sponsor, or its designated representatives will review and discuss the following items with the investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, CRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. A study manual with instructions for study compliance and CRF completion will be provided.

15.3. DOCUMENTATION

The PI and study staff has responsibility for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the Sponsor or the FDA at any time, and should consist of the following elements: patient files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the IRB, site, and Sponsor); and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

15.4. ACCESS TO SOURCE DATA

The PI will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. The CRF and related source documents will be reviewed in detail by the sponsor’s representative at each site visit. Only original source documents are acceptable for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the CRF, such as past history, secondary diagnoses, and concomitant medications. Other study records, such as correspondence with the sponsor and the IRB/EC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of the FDA or other regulatory agencies.

15.5. DATA COLLECTION

Case report forms must be submitted to the Sponsor for each patient enrolled in the study. CRF are to be completed in a neat, legible manner, using a black pen to ensure accurate interpretation of data, and faxed to a central location for a combination of Optical Character Recognition and manual entry. Any changes or corrections made on the CRF must be dated and initialed by the individual making the change, and subsequently reviewed and signed by the PI. When corrections are made, the original entry should be crossed out using a single line. Do not erase, overwrite, or use whiteout on the original entry. All data fields on the CRF must be completed.

15.6. PROTOCOL INTERPRETATION AND COMPLIANCE

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB approval. The Sponsor is responsible for submitting protocol amendments to the FDA as described in 21 CFR § 312.30 (Protocol Amendments). The Sponsor, or its designee, are always available to answer protocol- or patient-related questions.

15.7. STUDY MONITORING AND DATA COLLECTION

A representative from the Sponsor will visit the study center periodically to monitor adherence to the protocol and applicable FDA regulations, and the maintenance of adequate and accurate clinical records. Case report forms are reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The Sponsor or its designee is permitted to access patient medical records, laboratory data and other source documentation as needed to appropriately monitor the trial.

15.8. DISCLOSURE OF DATA/PUBLICATION

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by the FDA, the Sponsor or its designee and by the IRB.

The Study is designed as a multicenter study and not powered for analysis and presentation of Study results by individual Study sites. It is anticipated that the final results of this study will be submitted to a peer-reviewed scientific journal. Authorship on such a paper will be acknowledged with customary scientific practice. As such, without the expressed permission of the Sponsor, only clinical Study data relating the Study as a whole will be published. If permission is granted by Sponsor for publication of ancillary data from individual sites, prior to submission for publication of any manuscript or presentation of any poster, presentation, abstract or other written or oral material that describes the results of Study, Institution and/or PI shall provide Sponsor at least 60 days (or as otherwise specified in the sites executed Clinical Trail Agreement) to review any such materials. Such materials shall not divulge any of Sponsor's Confidential Information, and Institution and/or PI shall promptly remove any Confidential Information as requested by Sponsor. If requested by Sponsor, the PI and Institution shall delay the submission of any publication or

presentation up to 60 days from the date of Sponsor's request for such a delay. In addition, Sponsor has the right to require that any publication or presentation concerning the Study will acknowledge Sponsor's support.

15.9. ETHICAL CONSIDERATIONS

The investigator agrees to conduct this study in accordance with the International Conference on Harmonization (ICH) principles of Good Clinical Practice and with the Declaration of Helsinki (1989). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

15.10. INFORMED CONSENT

The PI assumes the responsibility of obtaining written informed consent for each patient or the patient's legally authorized representative before any study-specific procedures are performed.

Patients meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the investigator must exercise no selectivity with regard to offering eligible patients the opportunity to participate in the study. Patients or parents/legal guardians of all candidate patients will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper informed consent. Patients will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed consent will be documented by the use of a written consent form that includes all the elements required by FDA regulations and ICH guidelines. The sponsor or designee will review the informed consent prior to submission to the IRB/EC. The form is to be signed and dated by the patient or patient's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed consent form will be filed with the patient's medical records, and copy maintained with the patient's CRF. The date and time of time of the informed consent must be recorded in the source documents.

If an amendment to the protocol changes the patient participation schedule in scope or activity, or increases the potential risk to the patient, the informed consent document must be amended. Any amended informed consent must be reviewed by the sponsor or designee and approved by the IRB/EC prior to use. The revised informed consent document must be used to obtain re-consent from any patients currently enrolled in the study if the patient is affected by the amendment, and must be used to document consent from any new patients enrolled after the approval date of the amendment.

15.11. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI will forward copies of the protocol and consent form to be used for the study to the IRB/EC for its review and approval. A photocopy of the IRB/EC notification of

approval must be forwarded to the Sponsor or its designee before any investigational supplies will be shipped to the PI.

The PI will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior Sponsor and IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Copies of all study-related correspondence between the investigator and the IRB must be provided to the Sponsor, or its designee, by the investigator. The PI must promptly notify the IRB/EC of any SAE occurring at the site and of any IND safety reports received from the Sponsor, or its designee, and must copy the Sponsor, or its designee on that correspondence.

The investigator will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of patient risk involved in the study, but not less than once per year and at the completion or termination of the study.

15.12. PATIENT PRIVACY

The sponsor and the investigator affirm and uphold the principle of the patient's right to privacy. The Sponsor, it's designates and the investigator shall comply with applicable privacy laws.

To verify compliance with this protocol, the Sponsor, or its designee, will require that the investigator permit the Sponsor, or its designee's monitor to review the patient's original medical records. Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the investigator will obtain such permission in writing from the patient before the patient is entered into the study.

16. STOPPING THE STUDY

The sponsor may decide to stop the study at any point, for any reason.

APPENDIX A: SCHEDULE OF EVENTS

Visit	1	2	3	4		5		6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
	Surgery	Post-surgery MRI	Pre-leukapheresis	Leukapheresis	Radiation and Chemotherapy	Baseline Visit [b]	Enrollment	**Immunizations**																					End of Treatment	Survival Follow-up
								1	**2**	**3**	**4**	**5**		**6**		**7**			**8**			**9**			**10**				
						-1 wk		**Time 0[d]**	**day 10**	**day 20**	**2 Mo**	**4 Mo**	**6 Mo**	**8 Mo**	**10 Mo**	**12 Mo**	**14 Mo**	**16 Mo**	**18 Mo**	**20 Mo**	**22 Mo**	**24 Mo**	**26 Mo**	**28 Mo**	**30 Mo**	**32 Mo**	**34 Mo**	**36 Mo**	**On-going**
Temodar (Stupp Protocol)[a]																													
Consent to collect tumor	**X**																												
Collection of tumor	**X**																												
Consent to Study			**X**																										
History	**X[c]**		**X**																										
Enrollment & Randomization							**X**																						
Physical Exam						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Neurological Exam						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Vital Signs						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
KPS						**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
MRI of brain	**X**	**X[e]**				**X**					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
CBC and Differential			**X**			**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Blood Chemistry[f]			**X**			**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Urinalysis			**X**																									**X**	
Pregnancy test			**X**																										
anti-DNA[g]						**X**		**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Virology Testing[h]			**X**																										
Leukapheresis				**X**																									
Blood for Immune Monitoring[i]						**X**		**X**		**X**	**X**	**X**		**X**		**X**			**X**			**X**			**X**				
Injection of Study Drug[j]								**X**	**X**	**X**	**X**	**X**		**X**		**X**			**X**			**X**			**X**				
AE Assessment				**X**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Survival[k]																													**X**

Footnotes to Schedule of Events

[a)] See Appendix B for treatment guidelines

[b)] Tests done at the baseline visit complete Screening examinations. The patient must meet all eligibility criteria verified at screening to be enrolled in the investigational arm of the study. Patients with progressive disease at baseline, or who are otherwise ineligible for the investigational arm of the study, will be enrolled in the informational arm.

[c)] Limited history to assess potential study eligibility, including age, absence of prior malignancies including other brain cancers, no bilateral disease, no known HIV-1,2 infection, no conflicting prior treatments.

[d)] Time 0, the day of the first injection, takes place approximately 1 week after the baseline visit (Visit 5).

[e)] MRI done 1-3 days after surgery

[f)] Comprehensive metabolic panel, including electrolyte balance, and hepatic and renal functions.

[g)] Anti-DNA antibodies are measured as markers of induced autoimmunity.

[h)] Virology testing is performed prior to leukapheresis and includes the following: HbsAg, a-HIV-1, a-HIV-2, HIV-1p24Ag, a-HCV.

[i)] Ten (10) 10mL Green-Top tubes of whole blood plus one Red-Top tube are drawn at Time 0. Subsequent blood draws for immune monitoring are drawn prior to injection and require ten 10mL Green-Top tubes plus one Red-Top tube. After the blood draw, the tubes are shipped to the research laboratory of Cognate BioServices, Inc., Baltimore, MD, for development of immune monitoring tests.

[j)] A sufficient amount of DCVax-Brain or autologous PBMC is shipped to the site for up to 10 i.d injection visits (2 injections for each visit). Some patients may not receive 10 immunizations due to insufficient material.

[k)] Survival follow-up will be conducted through quarterly phone calls.

APPENDIX B

APPENDIX B: DETAILED TIMELINE FOR POST RADIATION PERIOD

Day	*Week*	Treatment
0	**0**	**Last day of radiation therapy**
14	**2**	**MRI**
15		*≥4 days rest*
16		
17		
18		
19		**Immunization #1**
20		*≥9 days rest*
21	**3**	
22		
23		
24		
25		
26		
27		
28	**4**	
29		**Immunization #2**
30		*≥9 days rest*
31		
32		
33		
34		
35	**5**	
36		
37		
38		
39		**Immunization #3**
40		*≥10 days rest*
41		
42	**6**	
43		
44		
45		
46		
47		
48		
49	**7**	
50		**1st Temodar cycle**
51		
52		
53		
54		
55		

APPENDIX C

APPENDIX C: GUIDELINES FOR TEMODAR USAGE

DETAILED TEMODAR USAGE GUIDELINES

Per the dosing guidelines on the Temodar® website and the Stupp article (Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma).

All patients:
With Radiation - 75 mg/m² daily, 7 days per week from the first to the last day of radiotherapy, 42 days, but for no longer than 49 days.

Adjuvant (Post Radiation) - Patients receive six or more cycles of adjuvant temozolomide according to the standard 5-day schedule every 28 days. For the first cycle the dose is 150 mg/m² daily and increased to 200 mg/m² daily beginning with the second cycle if no toxic effects.

Dose modifications for toxicity:
With Radiation - No dose reductions are recommended, however, dose interruptions may occur based on patient tolerance. The TEMODAR® dose can be continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x10^9/L, common toxicity criteria (CTC) non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 1.** PCP prophylaxis is required during the concomitant administration of TEMODAR® and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade ≤ 1).

Table 1. Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption[a]	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 and <100 x 10^9/L	<10 x 10^9/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count ≥ 1.5 x 10^9/L; platelet count ≥100 x 10^9/L; CTC non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting).
TMZ = temozolomide; CTC = Common Toxicity Criteria.

Adjuvant (Post Radiation) - Four weeks (or 10 weeks for DCVax-Brain patients) after completing the TEMODAR® + RT phase, TEMODAR® is administered for an additional 6 or more cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m² once daily for 5 days

followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m², if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of TEMODAR® should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to **Tables 2** and **3**.

Table 2. Temozolomide Dose Levels for Maintenance Treatment

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

Table 3. Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

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

a: TMZ dose levels are listed in **Table 2**
b: TMZ is to be discontinued if dose reduction to <100 mg/m 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.

APPENDIX D

APPENDIX D: CONSENT TO COLLECTION OF BRAIN TUMOR TISSUES FOR CLINICAL RESEARCH

REDACTED

APPENDIX E

APPENDIX E: DCVax®-BRAIN STUDY CONSENT

REDACTED

APPENDIX F

APPENDIX F: PERFORMANCE STATUS SCALES

Karnofsky Performance Scale[1]

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

References:

1. Karnofsky, DA: Meaningful clinical classification of therapeutic responses to anti-cancer drugs. Clin Pharmacol Ther 1961;2:709-712.

2. Stanley, KE: Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 1980;65:25-32.

APPENDIX G

APPENDIX G: MODIFIED GRADING OF INJECTION SITE REACTION TOXICITY

The following toxicity grading is for vaccine injection site reactions (dermatology/skin). It is quantitative, objective, more consistent, and works well for reporting skin site reaction as an AE:

Grade 0 None

Grade 1 Erythema and induration of treatment site of ≤2 cm of surrounding tissue accompanied by small ulceration.

Grade 2 Erythema and induration of treatment sites >2 to <4 cm of surrounding tissue and/or some surrounding rash; accompanied by large ulceration >2 to <4 cm.

Grade 3 Extensive (e.g., dermal sloughing) regional ulceration of ≥4 cm at each injection site.

Grade 4 Diffuse rash requiring hospitalization, I.V. support, and parenteral medication.

APPENDIX H

APPENDIX H: DATA MONITORING COMMITTEE CHARTER

REDACTED

APPENDIX I

APPENDIX I: NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 3.0

Found at: http://ctep.cancer.gov/forms/CTCAEv3.pdf

Protocol 020221 Summary of Changes

Protocol version, date	Main Characteristics or Changes in Trial Design
v1.0 – v3.2	• Open label study, under which only 3 subjects were enrolled. These 3 subjects are not part of the Phase III ITT population.
v4.0, 22 October 2007[1] **Original Protocol of Randomized Controlled Trial**	• Randomized, placebo-controlled design • Primary endpoint is PFS, OS is secondary endpoint • Crossover option for all subjects from both arms of the trial to receive DCVax®-L following tumor recurrence • Planned enrollment of 240 subjects, randomized 2:1
v5.2, 7 May 2012[2]	• Designated as Phase III (from Phase II) • Addition of several tertiary/exploratory endpoints
v6.0, 24 February, 2014[3]	• Addition of Absolute Lymphocyte Count as a covariate • Increase in sample size to 348 subjects
V6.1, 5 November 2014	• Addition of additional evaluations (including IDH-1 mutational status)
v7.0, 23 September 2020 **Final Protocol**	Several changes to conform to the Statistical Analysis Plan (SAP), dated 23 September 2020 • Primary endpoint: OS for newly diagnosed glioblastoma patients, compared to external controls • Secondary endpoint: OS for recurrent glioblastoma patients, compared to external controls • SAP included as Appendix to the Protocol • The SAP v1.0 governs all analyses for the study

[1] The Original Protocol also included an "Informational Arm" for subjects who failed to meet the eligibility criteria for enrollment in the trial. These patients were treated in a separate cohort outside the trial on a compassionate use basis.

[2] In this Protocol, new enrollment in the Information Arm cohort was terminated.

Also in this Protocol, a new separate "Pseudo-Progression Arm" cohort was established for patients who failed to meet the eligibility criteria for the trial because of apparent pseudo-progression. These patients were treated outside the trial on a compassionate use basis.

[3] This Protocol removed the Pseudo-Progression Arm.