A randomized, controlled phase II surgical trial to evaluate early immunologic pharmacodynamic parameters for the viral cancer therapy ofranergene obadenovec (VB-111) in patients with surgically accessible recurrent/progressive glioblastoma

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Coordinating Center: **Dana-Farber Cancer Institute**

Principal Investigator

Patrick Wen, MD
Dana-Farber Cancer Institute
Center for Neuro-Oncology
Boston, MA 02115-6084
Phone: (617) 632-2166
Fax: (617) 632-4773
Patrick_wen@dfci.harvard.edu

Co-Investigator

Timothy Cloughesy, MD
University of California, Los Angeles
Neuro-Oncology Program
Los Angeles, CA 90095
Phone: 310-825-5321
Fax: 310-825-0664
TCloughesy@mednet.ucla.edu

Biostatistician

Donatello Telesca, PhD

Responsible Research Nurse: **Lisa Doherty, APRN, BC, OCN**
Dana-Farber Cancer Institute
Lisa_Doherty@dfci.harvard.edu

DFCI Coordinating Center: **Kathryn Partridge & Christine McCluskey**
Research Project Managers
Dana-Farber Cancer Institute
NeuroOnc_Coor@dfci.harvard.edu

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STUDY SCHEMA

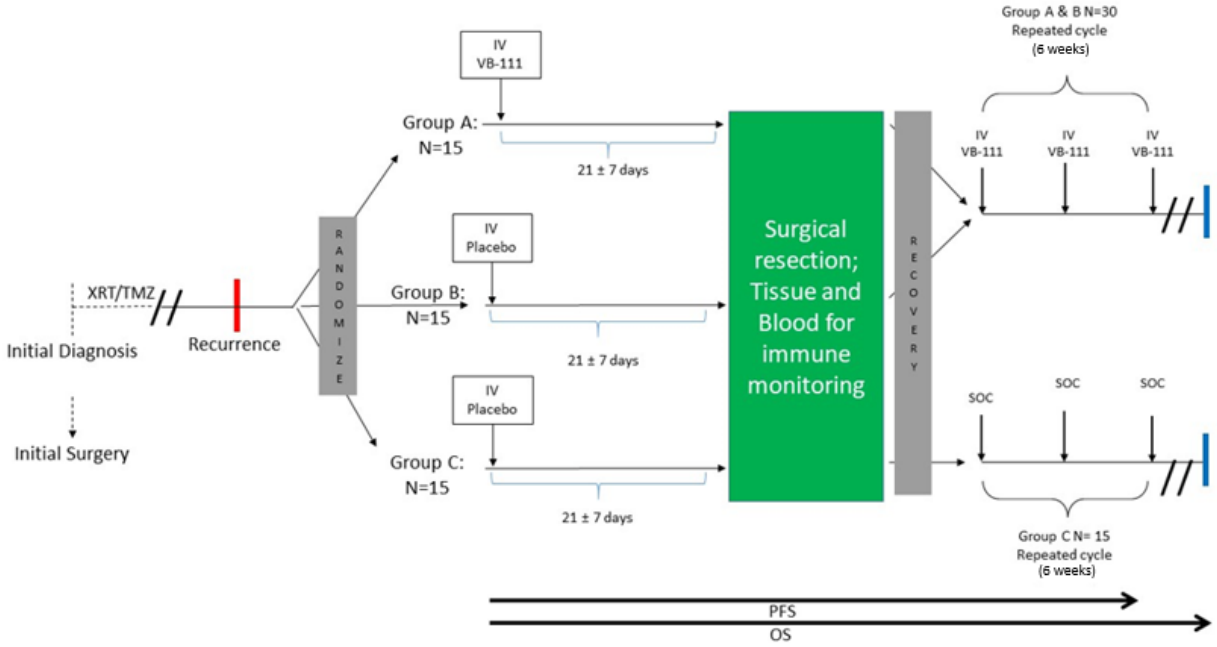

TABLE OF CONTENTS

1. OBJECTIVES 6
- 1.1 Study Design 6
- 1.2 Primary Objectives & Hypotheses 7
- 1.3 Secondary Objectives & Hypotheses 7
- 1.4 Exploratory Objectives 7

2. BACKGROUND 8
- 2.1 Glioblastoma 8
- 2.2 VB-111 9
- 2.3 Safety 11
- 2.4 Rationale 11

3. PARTICIPANT SELECTION 15
- 3.1 Inclusion Criteria 15
- 3.2 Exclusion Criteria 17
- 3.3 Inclusion of Women and Minorities 18

4. REGISTRATION AND RANDOMIZATION PROCEDURES 19
- 4.1 General Guidelines for DF/HCC Institutions 19
- 4.2 Registration Process for DF/HCC Institutions 19
- 4.3 General Guidelines for Other Investigative Sites 19
- 4.4 Registration Process for Other Investigative Sites 19
- 4.5 Unblinding and Step 2 Registration for All Sites 19

5. TREATMENT PLAN 20
- 5.1 Treatment Regimen 20
- 5.2 Pre-Treatment Criteria 22
- 5.3 Agent Administration 22
- 5.4 Trial Blinding/Masking 23
- 5.5 Stratification 23
- 5.6 Participant Evaluability 23
- 5.7 General Concomitant Medication and Supportive Care Guidelines 23
- 5.8 Duration of Therapy and Criteria for Removal from Study Treatment 25
- 5.9 End of Treatment Evaluation and Follow-Up 26
- 5.10 Long-Term Follow-Up and Study Completion 26
- 5.11 Participant Replacement Strategy 27

6. DOSE DELAY 27

7. ADVERSE EVENTS: REGULATORY AND REPORTING REQUIREMENTS 27
- 7.1 Anticipated Toxicities 27
- 7.2 Adverse Event Characteristics and Definitions 28
- 7.3 Adverse Event Reporting 29
- 7.4 Abnormal Laboratory Values 32
- 7.5 Procedures and Timeline for Reporting of Serious and/or Unexpected

Adverse Events 32
7.6 Handling of Serious Adverse Events 33
7.7 Expedited Reporting to the Food and Drug Administration (FDA) 34
7.8 Reporting to the NIH Office of Biotechnology Activities (OBA) 34
7.9 Reporting to the Institutional Biosafety Committee (IBC) 34
7.10 Expedited Reporting to Hospital Risk Management 34
7.11 Routine Adverse Event Reporting 34

8. INVESTIGATIONAL AGENT INFORMATION 34
8.1 VB-111 34

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES 38
9.1 Expanded TCR clones, TIL Density and TCR Overlap 38
9.2 Immunohistochemistry (IHC) Measurements 38
9.3 Immunophenotyping 39
9.4 Cell-Cycle Related Gene Signatures, Gene Expression Signatures and Somatic Mutations 39
9.5 Transgene and Viral Analysis 39

10. STUDY CALENDAR 42

11. MEASUREMENT OF EFFECT 45
11.1 Anti-Tumor Effect Definitions 45
11.2 Response Criteria for Target Lesions 46
11.3 Confirmatory Measurement/Duration of Response 47
11.4 Modified RANO (iRANO): Study Continuation Beyond Initial Progressive Disease 47
11.5 Radiology Review 50

12. Data Reporting/Regulatory Requirements 51
12.1 Data Reporting 51
12.2 Data Safety Monitoring 51
12.3 Multicenter Guidelines 51

13. STATISTICAL ANALYSIS PLAN 52
13.1 Study endpoints 52
13.2 Definitions of Analysis Sets 52
13.3 Sample Size Consideration 53
13.4 Efficacy Analysis 53
13.5 Safety Analyses 53
13.6 Exploratory Analyses 54
13.7 Baseline Characteristics and Demographics 54
13.8 Compliance (Medication Adherence) 54
13.9 Extent of Exposure 54
13.10 Procedure for Accounting for Missing, Unused and Spurious Data 55

14. PUBLICATION PLAN 55

REFERENCES 56

APPENDIX A: Karnofsky Performance Status.....60

APPENDIX B: Multi-Center Data and Safety Monitoring Plan 61

APPENDIX C: Reportable AE Coversheet 79

APPENDIX D: Drug Supply Request Form.....80

LIST OF TABLES

Table 1: Investigator's Choice Single Agent Standard of Care Treatments. 21
Table 2: Requirements and Timeline for Reportable AEs. .....**Error! Bookmark not defined.**
Table 3: VB-111 Preparation. 35
Table 4: Correlative Sample Summary. 40
Table 5: Summary of RANO Response Criteria. 47
Table 6: Imaging and Treatment After 1st Radiographic Evidence of PD. 50
Table 7: Study Data Submission Table. 51

1. OBJECTIVES

1.1 Study Design

This is a randomized, controlled, blinded, phase II, surgical trial to evaluate early immunologic pharmacodynamic parameters for the viral cancer therapy ofranergene obadenovec (VB-111) in participants with surgically accessible recurrent/progressive glioblastoma (rGBM). The principal goal of this study is to investigate if neoadjuvant VB-111 elicits a tumoral immunologic response, if the immune response can be sensitively monitored using tumor and peripheral blood immune cells, and if neoadjuvant VB-111 increases tumor-specific T cells. Please see Figure 1 for Schema.

Group A: VB-111 at $1x10^{13}$ VPs will be administered intravenously 21±7 days prior to surgery. Upon recovering from surgery (within 28-35 days after surgery), participants will receive intravenous VB-111 every 6 weeks. Upon evidence of contrast-enhancing progression, participants may initiate bevacizumab or biosimilar as needed for supportive care and will continue with VB-111 infusions until progression is supported by two consecutive time points of tumor growth.

Group B: Placebo will be administered intravenously 21±7 days prior to surgery. Upon recovering from surgery (within 28-35 days after surgery), participants will receive intravenous VB-111 every 6 weeks. Upon evidence of contrast-enhancing progression, participants may initiate bevacizumab or biosimilar as needed for supportive care and will continue with VB-111 infusions until progression is supported by two consecutive time points of tumor growth.

Group C: Placebo will be administered intravenously 21±7 days prior to surgery. Upon recovery from surgery, participants will receive standard of care treatment and every 6 weeks until evidence of progression is supported by two consecutive time points of tumor growth.

After recovering from surgery, participants will be evaluated every 6 weeks with radiographic imaging to assess response to treatment. The Response Assessment in Neuro-Oncology (RANO) criteria will be used as the efficacy endpoint of response rate. A modified RANO (iRANO) (as described in Section 11.4) will be used to evaluate response and progression in an exploratory fashion due to the tumor response patterns seen with immunotherapy treatment. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment with study therapy will continue until progression is supported by two consecutive time points of tumor growth, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, completion of 24 months of study therapy, or administrative reasons. After the end of treatment, each participant will be followed for 30 days for adverse event monitoring and 90 days for serious adverse event reporting. Participants who discontinue treatment for reasons other than disease progression will have post-treatment follow-up of disease status until disease progression, withdrawing consent or becoming lost to follow-up. All participants will be followed by telephone contact or medical record review for overall survival until death, withdrawal of consent, or the end of the study, whichever comes first.

Our hypothesis is that a functional immune defect exists within the T lymphocyte compartment in recurrent/progressive glioblastoma participants, and the neoadjuvant use of VB-111 will lead to:

1) increased tumor infiltrating T lymphocytes within the tumor; and 2) enhanced systemic specific T cell responses. The combination of tumor tissue, peripheral blood, and imaging evaluations should provide insight into immune activation, antitumor effect and toxicity with VB-111 in this population.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Study Calendar in Section 9.

1.2 Primary Objectives & Hypotheses

Primary Objective 1: To evaluate the influence of VB-111 on tumor infiltrating T lymphocyte (TIL) density in recurrent/progressive GBM participants.

We hypothesize that neoadjuvant VB-111 will increase tumor infiltrating T lymphocytes within the tumor and enhance systemic tumor-specific T cell responses compared to adjuvant and control tumors.

Primary Objective 2: To evaluate the safety and tolerability of intravenous VB-111 in progressive/recurrent GBM participants undergoing surgery.

Safety analysis will be based on toxicities and grades as defined by CTCAE version 5.0 criteria, including serious adverse events (SAEs). The attribution to drug, time-of-onset, duration of the event, resolution, and any concomitant medications administered will be recorded. AEs analyzed include but are not limited to all AEs, SAEs, and fatal AEs.

1.3 Secondary Objectives & Hypotheses

Secondary Objective 1: To estimate the 6-month progression-free survival (PFS6) in recurrent/progressive GBM participants treated with VB-111 (Group A and Group B) compared to control (Group C), using RANO criteria.

Hypothesis 1: We hypothesize that a greater percentage of participants who are treated with VB-111 will not have experienced tumor progression at 6 months after treatment.

Secondary Objective 2: To calculate the overall survival of recurrent/progressive GBM participants in each arm.

Hypothesis 2: We hypothesize that progressive/recurrent GBM participants treated with VB-111 will live significantly longer than Group C and/or historical controls of this participant population.

Secondary Objective 3: To evaluate the influence of VB-111 on peripheral T cell responses, specifically on expanded TCR clones.

Hypothesis 3: We hypothesize that specific subsets of TCR clones will expand in response to VB-111.

1.4 Exploratory Objectives

To evaluate the associations between exploratory biomarkers, clinical outcomes and adverse events which include:

- Exploring the influence of VB-111 on cell cycle-related genetic signatures or IFN-γ associated signatures within the tumor microenvironment and correlating with clinical responses.

- Exploring the influence of VB-111 on oligoclonal T-cell populations within tumor tissue and peripheral blood and correlating with clinical responses.
- Exploring the influence of VB-111 on specific MRI parameters, and correlating with tumor and peripheral blood immune responses.
- Estimating the efficacy of VB-111 by PFS and OS as defined by RANO.
- Estimating the efficacy of VB-111 by PFS6, PFS and OS as defined by iRANO.

2. BACKGROUND

2.1 Glioblastoma

Glioblastoma is the most common malignant primary brain tumor in adults [1]. Despite multimodal treatment with surgical resection, radiotherapy, and temozolomide, prognosis remains dismal with median progression-free survival of only 6.9 months and median overall survival of 14.6 months [2]. Following progression, salvage therapies have historically provided nominal benefit, with PFS6 rates under 10% [3-5].

The aggressive behavior of glioblastoma is in part due to its highly angiogenic and vascular nature, as well as its unique immunosuppressive microenvironment.

2.1.1 Angiogenesis

Angiogenesis via endothelial cell proliferation plays a pivotal role in the earliest phase of glioblastoma development [6] and serves as a key event in tumor growth and progression [7]. As a result, angiogenesis has been of particular interest in targeting tumor growth and the treatment of glioblastoma [8, 9]. While anti-angiogenic therapy such as bevacizumab, a humanized anti-vascular endothelial growth factor antibody, has shown promise as the latest drug approved for the management of glioblastoma in over a decade, it has failed to confer benefit in overall survival [10] as a monotherapy or in combination with chemotherapy [11]. Contending anti-angiogenic agents such as the small molecule inhibitors sunitinib and sorafenib have also failed to prolong PFS, at the cost of significant treatment-related toxicity [12, 13, 14, 15] and early termination of a phase 2 study based on interim analyses [16].

2.1.2 Immunologic Environment / Immunotherapy

Also unique to glioblastoma is an immunologically “cold” microenvironment which fosters immunosuppression [17] and antagonizes anti-tumor immune responses [18]. The role of T-cell infiltration in combating cancer has been increasingly recognized, as lymphocytes in the stroma of cancers such as melanoma, colorectal, and ovarian carcinoma have been associated with improved participant outcomes [19-24]. The presence of tumor-infiltrating lymphocytes (TILs) suggests an antitumor adaptive immune response and may impact survival in glioblastoma as well. However, the classical glioblastoma microenvironment has rare to non-existing infiltrating immune effector cells [25].Immunosuppressive changes are similarly evident in the peripheral blood of glioblastoma participants. A paucity of circulating CD4-positive T cells and an increased proportion of T regulatory lymphocytes [26] serve to suppress anti-tumor activity through inhibition of cytotoxic cytokine secretion by effector lymphocytes [27, 28]. Even if lymphocytes and other immune cells are able to infiltrate the glioblastoma microenvironment [29, 30], an immunosuppressive tumor milieu likely prevents successful immune-mediated tumor eradication.

An emerging strategy in the treatment of various neoplasms involves the stimulation of an immune response against malignant cells. In order to unlock and maximize the potential implications of immune-based therapies, we seek to effectively induce an anti-tumor T cell response and switch glioblastoma from a "cold" into "hot" tumor with VB-111 and characterization of tumor T-cell infiltration and inflammatory gene expression signatures elicited by VB-111.

2.1.3 Gene therapy

Viral gene therapy holds significant potential in the treatment of disease due to its ability to achieve prolonged expression of target therapies and circumvent issues with production of recombinant proteins. However, limitations of therapy include duration of expression, induction of immune response, and lack of target-tissue specificity [31]. Adenoviruses have gained favor in gene therapy, due to their advantage as a biologically safe vector with a large transgene insert capacity [32] and several studies in glioblastoma have administered adenovirus intratumorally or peritumorally [33-36], however other than VB-111 few have attempted systemic administration [37].

2.2 VB-111

Ofranergene obadenovec (VB-111) is a vascular-targeting anti-cancer gene-therapy with a dual mechanism of vascular disruption and induction of a tumor-directed immune response.

2.2.1 Mechanism of Action

VB-111 is comprised of a non-replicating Adenovirus (Ad-5, E1-deleted) which carries a pro-apoptotic human Fas-chimera transgene (Fas and human TNF receptor 1), under the control of a modified murine pre-proendothelin promoter (PPE-1-3x).

The modified murine promoter contains a hypoxia-response element that is upregulated under hypoxic conditions, such as in angiogenic endothelium. Specificity of expression is further induced by endogenous TNF-α, which is enriched within the tumor milieu and interacts with the Fas-TNF receptor 1 to promote apoptosis [38, 39]. This provides selective vascular disruption and tumor starvation [40-42], thereby minimizing toxicity to other tissues during systemic intravenous administration. Additionally, penetration of the blood brain barrier is not necessary since the transgene targets endothelial cells on the luminal wall of neovasculature.

In response to viral infection and apoptosis, local and systemic antitumor immune responses activate cytokine release and stimulate antigen presenting cell activity [43]. Local infiltration of CD8 T cells into tumor is observed with systemic administration of VB-111 in participants with ovarian cancer and is accompanied by apoptosis of tumor cells.

2.2.2 Preclinical and Clinical Trial Data

Preclinical studies have confirmed the antitumor activity of VB-111 in mouse models of Lewis lung carcinoma [40], mouse models of B16 melanoma [40], and nude rat glioblastoma xenografts [44].

Completed Phase 1 and Phase 2 clinical trials have shown overall survival benefit with VB-111 across multiple tumor types, including recurrent glioblastoma, platinum-resistant ovarian cancer, and radioiodine-refractory thyroid cancer.

A Phase 1 all-comers study in participants with advanced solid tumors demonstrated that VB-111 was safe and well-tolerated up to $1x10^{13}$ VPs, with maximal tolerated dose not reached [45]. No drug-related serious adverse events were observed. In an exploratory post-hoc analysis, evidence of anti-tumor activity was demonstrated after a single-dose administration, with a dose-dependent response in median overall survival across a range of tumor types. Median overall survival in lower dose was 173 days vs not reached in the high-dose $1x10^{13}$ VPs cohort (p=0.0098). Median follow-up in this cohort was 487 days.

A Phase 2 study in participants with recurrent GBM demonstrated a survival benefit for participants treated with VB-111 monotherapy that was continued upon progression with combination treatment of VB-111 and bevacizumab (VB-111 Primed Combination) compared with participants treated with limited exposure of VB-111 (LE), and compared with literature reports of recurrent glioblastoma (rGBM) participants receiving bevacizumab monotherapy. Median PFS was 83 vs 56 days for the Primed Combination vs LE group (p=0.01; HR 0.46 [95% CI 0.23-0.91]). Median OS was significantly greater in the Primed Combination vs LE group (414 vs 223 days) (hazard ratio 0.51 [95% CI 0.26-0.99]; p=0.043). The historical control, constructed from a meta-analysis of 694 rGBM participants treated with bevacizumab monotherapy across 8 studies, showed a median overall survival (OS) of 32 weeks (224 days), significantly lower than the median OS in the Primed Combination group (p=0.0295). The 12-month OS was 57% in the Primed Combination group vs 24% in the historical control (p=0.03).

A Phase 3, multisite, international, randomized, open-label, controlled trial in participants with rGBM after first or second progression (GLOBE) was performed to confirm earlier findings. However, the sequencing of VB-111 and bevacizumab was unlike the initial Phase 2 study. In this study, bevacizumab was given together with VB-111 instead of upon progression. Participants were randomized 1:1 to receive VB-111 at 10^{13} VPs q8w in combination with bevacizumab 10mg/kg q2w (combination arm) or monotherapy with bevacizumab 10mg/kg q2w (control arm). The primary endpoint of OS and secondary endpoints of objective response rate (ORR) by Response Assessment in Neuro-Oncology (RANO) criteria, Progression Free Survival (PFS) and safety were investigated in two hundred fifty-six participants enrolled in 57 sites. In the combination vs the control arm, median exposure to VB-111 was 4 months. Median OS was 6.8 vs 7.9 months (HR 1.2 [95% CI 0.91-1.59, p=NS]). ORR was 27.3% vs 21.9% (p=0.26), respectively. VB-111 in combination with bevacizumab failed to increase OS. We believe that lack of VB-111 monotherapy priming may explain the difference from the favorable Phase 2 outcome.

To further explore the role of priming, this study will explore the effects of single-dose neo-adjuvant VB-111, followed by adjuvant treatment. The primary endpoint will be to evaluate whether neoadjuvant VB-111 increases the density of tumor infiltrating T cells (TIL) within recurrent glioblastoma. To assess the baseline TIL density, we extracted genomic DNA from 62 GBM samples (newly diagnosed and recurrent). The samples were subjected to next generation T cell receptor sequencing at Adaptive Biotechnologies (Seattle, WA). The average TIL density was 0.50 +/- 0.68 % T cells/nucleated cell (obtained from fresh-frozen tumor tissue). No statistically significant differences in TIL density were found between recurrent and newly diagnosed glioblastoma samples.

2.2.3 Ongoing Clinical Trials

An ongoing phase III trial with VB-111 is being conducted in recurrent platinum-resistant ovarian cancer.

2.3 Safety

Main Safety Features

- Deletion of the wildtype E1 transcriptional unit renders the virus replication incompetent
- Vector incorporates a tissue-specific promoter (expression of transgene is limited to angiogenic endothelial cells
- The life cycle of the virus does not involve integration into the host genome; it replicates as episomal elements in the nucleus of the host cell, eliminating the risk of insertional mutagenesis
- Clinical data supports minimal vector shedding

2.3.1 Toxicology

Pre-clinical toxicology and biodistribution studies with single doses of VB-111 as well as repeat doses in mice demonstrated a safe toxicity profile. A completed phase 1 trial found VB-111 to be safe and well-tolerated, with transient fever as the most frequent adverse event and no severe adverse events observed.

2.3.2 Biodistribution

In preclinical evaluations, vector DNA was detected in all blood and tissue samples collected from mice in both non-tumor bearing and tumor bearing high dosed groups. The elimination rate was one magnitude of order in tissues and two magnitudes of order in blood between Day 5 and Day 91. Transgene expression was not found in non-tumor bearing mice. Expression was observed by RT-PCR only in lungs of tumor-bearing mice, demonstrating specificity of the treatment to the Lewis lung tumor mice [44].

In a completed phase 1 trial, mean levels of adenovirus vector DNA found in whole blood showed a dose-dependent effect. By 2 months after dosing, levels of Ad-5 decreased by at least 3-log or were undetectable. Detectable levels of Ad-5 in the urine were present only within the initial 6 hours after intravenous administration of VB-111. In a participant with esophageal cancer, transgene expression was found in subcutaneous metastasis aspirates up to Day 28 [45].

2.4 Rationale

2.4.1 Rationale for VB-111 Therapy for Glioblastoma

Glioblastoma is one of the most aggressive human cancers, with very few long-term survivors and no definitive cure. Due to its invasive nature of infiltrating surrounding healthy brain parenchyma, complete surgical excision is impossible. Radiotherapy and chemotherapy target remaining cells with limited effectiveness and inevitable recurrence.

Immunotherapy is well-suited to target isolated pockets of infiltrating tumor cells in the brain. There has been a long-standing interest in applying tumor immunotherapy approaches to primary brain tumors. Unfortunately, these efforts have largely shown little in the way of objective therapeutic efficacy due to limitations of the blood brain barrier, poor tumor penetration, and inflammatory response.

Targeting glioblastoma vasculature by gene therapy with VB-111 has several potential advantages compared with direct cancer cell targeting:

1. Adenoviral vectors have been widely used clinically in a variety of gene therapy products and indications, including glioblastoma
2. TNFα, which activates the Fas-chimera transgene, is abundant in the tumor

microenvironment and allows VB-111 to trigger targeted apoptosis, resulting in less tissue damage

3. Apoptotic tumor epitopes promote an immune response with the viral vector operating synergistically as an immune adjuvant. By using a specific endothelial promoter, which is not expressed in immune cells, the anti-transgene immune response can be avoided, thus eliminating immune reactions to recurrent treatments
4. Because of the inherent genetic stability of resting and angiogenic vascular endothelial cells, there is less susceptibility than in tumor cells to the emergence of drug resistance
5. Evidence for an immune therapeutic effect of VB-111 is based on a viral mediated immune mechanism:
   - Treatment with VB-111 is associated with a serum cytokine profile that correlates with a clinical fever response and participant OS
   - IHC staining of biopsies from ovarian cancer participants show recruitment of CD8 T-cells in tumor from participants treated with VB-111, but not in untreated control samples
   - Preclinical histology shows mononuclear infiltrate in tumor sample from VB-111-treated mice
   - Ex-vivo analysis of tumor specimens from mice induced with a U251 GBM model demonstrate tumor microglia recognition of VB-111 in vivo through cytokine release that promotes a cytotoxic T cell response

Glioblastoma is of particular interest for VB-111 therapy for several reasons:

- Recurrent glioblastoma is a disease with grave prognosis and a significant unmet therapeutic clinical need
- Glioblastoma is a highly vascularized tumor for which angiogenesis is critical to development and progression; vascular inhibition may be a powerful anti-tumor strategy
- VB-111 demonstrates efficacy in pre-clinical glioma rat models
- VB-111 demonstrates safety and tolerability in Phase 1, Phase 2 and Phase 3 rGBM clinical trials

2.4.2 Rationale for Dose Selection

The maximal administered dose in the Phase 1 Advanced Solid Tumors trial (GT-111001), Phase 1/2 Recurrent GBM trial (VB-111-122), Phase 2 Differentiated Thyroid Cancer trial (VB-111-PN-103) and Phase 3 Recurrent GBM trial (GLOBE) was $1x10^{13}$ VPs. The drug was well tolerated and MTD was not reached. No excess toxicity was seen. In review of tumor response and survival data, a dose response signal with improvement in OS in participants who received $1x10^{13}$ VPs, as detailed above.

Manufacturing VB-111 at doses higher than $1x10^{13}$ VPs has proven to be challenging.

Therefore, based on the data available and manufacturing capacity, $1x10^{13}$ VPs has been selected as the ideal dose to treat participants in this trial.

2.4.3 Rationale for Dose Schedule

Since VB-111 is a non-replicating Ad-5 vector, repeated dosing may prolong its desired effect on vasculature, resulting in attenuation of tumor growth. All antiangiogenic drugs currently approved

for cancer therapy were found to be efficacious and are approved for multiple dose regimens [46-48]. Therefore, repeated dosing may be necessary for providing clinically significant benefit of VB-111 treatment.

2.4.4 Rationale for Decisions on Drug Discontinuation

The RANO criteria were developed to standardize imaging response evaluation in brain tumor clinical trials. However, novel immune therapies have led to challenges in assessing nonspecific contrast enhancement which may not be a true surrogate of tumor response, and also for non-enhancing tumor. In radiographic assessments of immune therapy for solid tumors, it has been recently recognized that early increase in lesion size and/or appearance of new lesions may occur in the presence of anti-tumor activity. This is evident when the drug is continued, followed by regression of tumor and improved clinical outcomes [49].

Based on this premise, immune-related response criteria (iRANO) have been suggested to incorporate new lesions into the total disease burden and require two consecutive time points of tumor growth to support determination of true progression of disease [50].

In the VB-111 phase 2 trial in recurrent glioblastoma (VB-111-122), several (3 of 12) participants developed new lesions which coincided with regression of tumor burden. Additionally, there were 12 participants with initial tumor growth followed by tumor regression or stabilization. Upon review of these data, it was suggested that a similar phenomenon to that seen in immunotherapy may occur with VB-111 in glioblastoma; thus, further treatment with VB-111 may provide improved clinical outcomes. Indeed, analysis of the phase 2 data showed that participants who continued to receive combination of VB-111 with bevacizumab after progression on VB-111 monotherapy—resulting in greater exposure to VB-111—had a favorable overall survival of 414 days vs 223 days in participants who stopped VB-111 at the first sign of RANO progression ($p=0.04$) [51]. Additionally, participants with contained progression on bevacizumab therapy have few further effective therapeutic alternatives, leading many providers to continue bevacizumab post-progression, in particular to avoid a rebound effect that has been documented post-bevacizumab cessation [52].

Based on these observations and experience with immunotherapy, participants with RANO-based progression and non-confirmed T2/FLAIR progression should remain on therapy. In this trial, bevacizumab or biosimilar may be added as symptomatic therapy for edema, mass effect or upon evidence of contrast-enhancing progression with the knowledge that its use does not benefit overall survival.

2.4.5 Rationale for Endpoints

2.4.5.1 Biomarker and Expression of Transgene Endpoints

Despite clinical activity of immunotherapies across a range of cancer types, the majority of participants fail to respond while immune mechanisms remain incompletely defined. To maximize the impact of therapy, well-characterized biomarkers are needed. We will correlate biomarkers with pharmacodynamic activity and bioactivity of VB-111, in search of a novel tumor tissue-based assay that may predict efficacy of VB-111, allow for monitoring of response, and identify subclinical immune-driven toxicity.

Changes in the local and systemic immune environment have been observed with VB-111 in preclinical models and clinical trials. Orthotopic U251 tumor microglia and T cell co-cultures in mice 6 hours after VB-111 administration exhibited a significant increase in several cytokines

correlating with overall survival, including IL-1R17α, IL-1α, MIP1α, and TNFα ($p<0.05$). They also demonstrated decrease in immunosuppressive cytokines, including IL-10, IL-4, IL-3, and IL-5 [53]. A human phase 1 trial revealed variability in cytokine and cytokine receptor levels. IL-6 demonstrated a transient 100-fold increase at 6 hours after dosing, correlating with concurrent fever. Statistically significant small transient increases were also noted in sCD54 ($p=0.03$) and TNFR-2 ($p=0.002$) at several time points over 28 days after dosing [45].

In this study, TIL density and TCR clonality will be quantitatively assessed with next generation TCR sequencing [54]. Expansion of TCR clones can be compared in VB-111 neoadjuvant vs placebo followed by postoperative VB-111.

Tumor and peripheral blood gene expression signatures and somatic mutations will be measured by RNA-seq and Exome sequencing. Cell-cycle related gene signatures will be measured by RNA-seq and Nanostring IO360.

Tumor and peripheral blood T cell subsets and activation markers will be assessed with mass cytometry high dimensional analysis to identify immune cell subsets that expand or contract in an unbiased fashion during treatment.

Tumor quantification of PD-1, PD-L1, CD3, CD4, CD8, Iba-1, Ki-67 will be measured by immunohistochemistry of FFPE tissue. Multiplex immunofluorescence will be used to spatially quantitate TIL in the tumor microenvironment.

VB-111 is an anti-angiogenic agent developed by VBL based on an adenovirus vector. It is a non-replicating E1 deleted, Adenovirus 5, carrying a pro-apoptotic human Fas-chimera (transgene) under the control of a modified murine promoter (PPE-1-3x). The transgene is specifically expressed in angiogenic endothelial cells. In this study, we will explore and validate the presence and expression of viral transgene in the tumor tissue.

2.4.5.2 Safety Endpoints

A primary objective of this study is to characterize the safety and tolerability of VB-111 in the pre- and post- operative settings in surgically resectable recurrent glioblastoma. Safety analysis will be based on toxicities and grades as defined by CTCAE version 5.0 criteria, including serious adverse events (SAEs). The attribution to drug, time-of-onset, duration of the event, resolution, and any concomitant medications administered will be recorded. AEs analyzed include but are not limited to all AEs, SAEs, and fatal AEs.

2.4.5.3 Efficacy Endpoints

Primary efficacy endpoint will be T lymphocyte (TIL) density, and the secondary efficacy endpoint PFS6 will be measured using RANO criteria. RANO criteria [55] as assessed by the investigator will be used to determine eligibility, make treatment decisions, and determine progression. KPS [Appendix A] as assessed by the investigator will be used to determine clinical progression. OS will be calculated based on time-to-event outcome.

3. PARTICIPANT SELECTION

Screening evaluations are detailed in Study Calendar (Section 10). The participant must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements of informed consent. The signed informed consent must be obtained from the participant prior to enrollment. All assessments are to occur within 28 days of registration except where otherwise noted.

Following registration, any additional laboratory assessments prior to start of treatment will not be used to reconfirm eligibility. Please refer to Section 6.0 Dose Delay for toxicity management between registration and start of study treatment.

3.1 Inclusion Criteria

3.1.1 Histologically confirmed World Health Organization Grade IV malignant glioma (glioblastoma or gliosarcoma).

3.1.2 First or second progression of glioblastoma/gliosarcoma (according to RANO criteria) following standard of care treatment upon initial diagnosis with radiation.

3.1.3 Measurable disease by RANO criteria at progression.

3.1.4 The maximal tumor volume at baseline meets the following criteria as determined by a local site investigator or surgeon: Longest diameter ≤ 4CM.

3.1.5 Surgically resectable disease at progression.

3.1.6 An interval of the following durations prior to randomization:

- At least 28 days from prior surgical resection, or 7 days from stereotactic biopsy
- At least 12 weeks from prior radiotherapy, unless there is unequivocal histologic confirmation of tumor progression
- At least 23 days from prior chemotherapy
- At least 42 days from nitrosureas
- At least 42 days from other anti-tumor therapies (including vaccines)
- At least 28 days from immune checkpoint blockade
- At least 28 days - or 5 half-lives - from any investigational agent, whichever is shorter.

NOTE: no wash-out period required from TTF.

3.1.7 All clinically significant toxic effects of prior therapy must have recovered to grade 0 or 1 or pre-treatment baseline. Allowable exceptions are: alopecia, lymphopenia, and any laboratory value listed elsewhere in the inclusion criteria (provided it meets that criterion's requirements). Please contact the Overall Principal Investigator, Dr. Patrick Wen, for questions regarding exceptions to this criterion.

3.1.8 Corticosteroid use at or less than dexamethasone 2mg daily. Participants should be on a stable or decreasing dose for at least 7 days prior to randomization.

3.1.9 Age ≥ 18 years on day of signing informed consent

3.1.10 KPS ≥ 70% (see Appendix A)

3.1.11 Adequate bone marrow, liver, and renal function according to the following criteria:

- Absolute neutrophil count ≥ 1,500 cells/mL ~ 1.5 K/μL
- Platelets ≥ 100,000 cells/mL ~ 100 K/μL
- Total bilirubin ≤ 1.5 X institutional ULN **OR** Direct bilirubin ≤ institutional ULN for subjects with total bilirubin levels > 1.5 institutional ULN
- Aspartate aminotransferase (AST) ≤ 2.0 x ULN
- Serum creatinine level ≤ ULN **or** creatinine clearance ≥ 50 mL/min for participants with creatinine levels above normal limits (calculated by the Cockcroft-Gault formula)

3.1.12 Ability to understand and willingness to sign a written informed consent document

3.1.13 Availability of 10 unstained formalin-fixed paraffin-embedded slides.

3.1.14 Patients must be able to tolerate MRIs.

3.1.15 MRI within 14 days prior to registration.

NOTE: *Due to the fact that the screening MRI will not be used for response purpose, participants may be registered if screening MRI is > 14 days of registration if prospective approval is received from Overall PI, Dr. Patrick Wen (for prospectively approved circumstances an eligibility exception will not need to be filed).*

3.1.16 Women of childbearing potential must have a negative serum beta-human chorionic gonadotropin urine or serum pregnancy test within 72 hours prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

NOTE: *Women are considered postmenopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.*

3.1.17 Males and females of childbearing potential must utilize a standard contraception method throughout the trial and up to 120 days after the last dose of treatment on study.

NOTE*: Women of childbearing potential and men with female spouses of childbearing potential must agree to use two methods of reliable contraception simultaneously or to practice complete abstinence from heterosexual contact prior to study entry, while receiving treatment, and for 4 months after undergoing treatment. One method must include a highly effective method such as an intrauterine device, hormonal (birth control pills, injections or implants), tubal ligation or partner's vasectomy. The other method can be an additional hormonal therapy or barrier method such as a male condom, diaphragm or cervical cap. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately.*

3.2 Exclusion Criteria

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

3.2.2 Has tumor primarily localized to the brainstem or spinal cord

3.2.3 Has presence of diffuse leptomeningeal disease or extracranial disease.

3.2.4 Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to first study treatment

3.2.5 Minor surgical procedure (e.g. stereotactic biopsy or shunt placement) within 7 days of first study treatment, placement of vascular access within 2 days of first study treatment

3.2.6 Expected to have surgery other than the neurosurgical procedure intended for the GBM lesion during study treatment period

3.2.7 Prior stereotactic radiotherapy (Note: those who have had biopsy proven tumor recurrence at a site of SRS treatment should be considered eligible if approved by the study central Investigator)

3.2.8 Prior anti-angiogenic therapy including VEGF sequestering agents (i.e. bevacizumab, aflibercept, regorafenib, etc.) or VEGFR inhibitors (cedirinib, pazopanib, sunitinib, sorafenib, etc.)

3.2.9 Prior administration of the study drug VB-111

3.2.10 Concomitant medication that may interfere with study results (e.g. immunosuppressive agents other than inhaled, topical or intra-articular steroids or a stable or decreasing dose of oral corticosteroids of up to <2 mg/day dexamethasone equivalent)

3.2.11 Known active second malignancy. Exceptions include non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Participants are not considered to have currently active malignancy if they have completed anticancer therapy and have been disease free for greater than 2 years prior to screening

3.2.12 Uncontrolled intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.13 History of stroke or transient ischemic attack within 6 months prior to randomization

3.2.14 Evidence of CNS hemorrhage CTCAE grade 2 or above on screening MRI

3.2.15 Active cardiac disease within 6 months prior to randomization (i.e. acute coronary syndrome, unstable angina, New York Heart Association grade II or greater congestive heart failure, or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment)

3.2.16 Significant vascular disease within 6 months prior to randomization (e.g. aortic aneurysm requiring surgical repair, peripheral arterial thrombosis, symptomatic peripheral vascular disease)

3.2.17 History of venous thromboembolism CTCAE version 5.0 grade 3 or greater

3.2.18 Known proliferative and/or vascular retinopathy

3.2.19 Inadequately controlled hypertension (defined as systolic blood pressure > 150mmHg and/or diastolic blood pressure > 100mmHg) within 1 week of randomization

3.2.20 History of pulmonary hemorrhage/hemoptysis ≥ grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 6 months of randomization.

3.2.21 History of active gastrointestinal bleeding within 6 months prior to randomization.

3.2.22 History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)

3.2.23 Current or recent (within 10 days of study randomization) use of aspirin > 325mg/day, clopidogrel > 75mg/day or equivalent. Therapeutic or prophylactic use of anticoagulants is allowed

3.2.24 Known liver disease (alcoholic, drug/toxin induced, genetic or autoimmune)

3.2.25 History of gastrointestinal perforation or abscess

3.2.26 Positive testing to any of the following viruses: HIV, HBV, HCV within the last 6 months. Exceptions include participants with serology positive for HBV indicating past exposure but without evidence of active infection (e.g. negative PCR)

3.2.27 History of intracranial abscess within 6 months prior to randomization

3.2.28 Serious non-healing wound, active ulcer, or untreated bone fracture

3.2.29 Pregnant or breastfeeding participants

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

The eligibility checklist(s) and all pages of the consent form(s) will be faxed to the ODQ at 617-632-2295 or emailed to their central or designee. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

An email confirmation of the randomization assignment will be sent to the registering site's study pharmacist and the lead site's Unblinded Contact (or back-up) immediately following the registration and/or randomization.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed. And refer to Appendix B (DSMP), Section 3.7.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center at Neuro_Coor@dfci.harvard.edu to verify slot availabilities. A list of the required forms for registration can be found in Appendix B (DSMP), Section 3.7.

Following registration, participants must begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

Refer to Appendix B (DSMP), Section 3.7.

4.5 Unblinding and Step 2 Registration for All Sites

Refer to Appendix B (DSMP), Section 3.7.4.

5. TREATMENT PLAN

This is a randomized, controlled, blinded, phase II, surgical trial to evaluate early immunologic pharmacodynamic parameters for the viral cancer therapy VB-111 in participants with surgically accessible recurrent/progressive glioblastoma (rGBM).

5.1 Treatment Regimen

Participants will be screened for eligibility up to 14 days prior to randomization. They will be sequentially randomized to one of three groups in a 1:1:1 ratio of the Neoadjuvant/Adjuvant arm (Group A), Adjuvant arm (Group B), and Control arm (Group C).

Group A (Neoadjuvant/adjuvant): Fifteen participants will receive VB-111 at $1x10^{13}$ VPs intravenously 21±7 days prior to surgery. Tumor samples will be obtained at time of surgery, and tissue (fresh, frozen and FFPE) will be processed to achieve primary, secondary and exploratory objectives. Upon recovering from surgery (within 28-35 days after surgery), participants will resume single agent intravenous VB-111 every 6 weeks until tumor progression is supported by two consecutive time points of tumor growth (based on RANO criteria) or adverse event requiring discontinuation of study drug. Upon initial evidence of contrast-enhancing progression, and if clinically stable, participants may continue with VB-111 infusions. Bevacizumab or biosimilar may be used as supportive care if clinically indicated. Blood samples will be obtained as pharmacodynamics markers throughout the study. Dose holds and symptomatic management will occur based on preset adverse event determination. DLTs will not be determined. The toxicity evaluation period will begin with registration and extend to 30 days after the last treatment day. Participants will be followed for MRI changes, clinical exam and steroid doses from the registration period until the second progression. After tumor progression is confirmed on the second consecutive MRI, VB-111 will stop and participants will be followed every 3 months for vital status until death.

Group B (Adjuvant): Fifteen participants will receive Placebo intravenously 21±7 days prior to surgery. Tumor samples will be obtained at time of surgery, and tissue (fresh, frozen and FFPE) will be processed to achieve primary, secondary and exploratory objectives. Upon recovering from surgery (within 28-35 days after surgery), participants will receive single agent intravenous VB-111 every 6 weeks until tumor progression is supported by two consecutive time points of tumor growth (based on RANO criteria) or adverse event requiring discontinuation of study drug. Upon evidence of contrast-enhancing progression, and if clinically stable, participants may continue with VB-111 infusions. Bevacizumab or biosimilar may be used as supportive care if clinically indicated. Blood samples will be obtained as pharmacodynamics markers throughout the study. Dose holds and symptomatic management will occur based on preset adverse event determination. DLTs will not be determined. The toxicity evaluation period will begin with registration and extend to 30 days after the last treatment day. Participants will be followed for MRI changes, clinical exam and steroid doses from the registration period until the second progression. After tumor progression is confirmed on the second consecutive MRI, VB-111 will stop and participants will be followed every 3 months for vital status until death.

Group C (Control): Fifteen participants will receive Placebo intravenously 21±7 days prior to surgery. Tumor samples will be obtained at time of surgery, and tissue (fresh, frozen and FFPE) will be processed to achieve primary, secondary and exploratory objectives. Upon recovering from surgery (within 28-35 days after surgery), participants will receive standard of care treatment until evidence of progression as determined in Group A and Group B.

Since there are various treatment alternatives for recurrent glioblastoma, the Investigator may choose any of the single agent treatments for participants randomized to the standard of care arm listed in Table 1 for the control treatment arm. When selecting the treatment, the Investigator should take into consideration the participant's prior treatment (e.g. participants who had received prior lomustine should not receive it again) and clinical status following surgical resection of the tumor.

Table 1: Investigator's Choice Single Agent Standard of Care Treatments.

Single Agent Treatment	**Dose**
Lomustine	(Oral [PO]) 110mg/m2 every 6 weeks is suggested
Temozolomide	(PO or IV) Initial dose of 150mg/m2 once daily for 5 consecutive days per 28-day treatment cycles, may be increased to 200mg/m2 once daily for 5 consecutive days in the following 28-day treatment cycles
Temozolomide metronomic	(PO) 50mg/m2 once daily continuously
Bevacizumab or Biosimilar	(IV) 10mg/kg every 2 weeks

After recovering from surgery, participants will be evaluated every 6 weeks with radiographic imaging to assess response to treatment. The Response Assessment in Neuro-Oncology (RANO) criteria will be used as the efficacy endpoint of response rate. A modified RANO (iRANO) (as described in Section 11.4) will be used to evaluate response and progression in an exploratory fashion due to the tumor response patterns seen with immunotherapy treatment (e.g., tumor flare). Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI CTCAE version 5.0. Treatment with study therapy will continue until documented disease progression supported by two consecutive time points of tumor growth, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, completion of 24 months of study therapy, or administrative reasons. After the end of treatment, each participant will be followed for 30 days for adverse event monitoring and 90 days for serious adverse event reporting. Participants who discontinue treatment for reasons other than disease progression will have post-treatment follow-up of disease status approximately every 8 weeks until disease progression, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone contact or medical record review for overall survival until death, withdrawal of consent, or the end of the study, whichever comes first.

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

5.2 Pre-Treatment Criteria

The pre-treatment criteria for C1D1 and subsequent cycles is listed below:

- Adequate bone marrow, liver, and renal function according to the following criteria:
    - Absolute neutrophil count ≥ 1,500 cells/mL ~ 1.5 K/μL
    - Platelets ≥ 100,000 cells/mL ~ 100 K/μL
    - ≤ 1.5 X institutional ULN **OR** Direct bilirubin ≤ institutional ULN for subjects with total bilirubin levels > 1.5 institutional ULN
    - Aspartate aminotransferase (AST) ≤ 2.0 x ULN
    - Serum creatinine level ≤ ULN **or** creatinine clearance ≥ 50 mL/min for participants with creatinine levels above normal limits (calculated by the Cockcroft-Gault formula)
- For women, a negative pregnancy test
- No intercurrent illness or medical condition that, in the opinion of the Investigator, may cause excess risk for the participant's continued treatment with the study drug

In any case of doubt or failure to meet the criteria listed above, the investigator should contact the Overall Principal Investigator, Dr. Patrick Wen, and/or DFCI Neuro Oncology Coordinating Center for instructions on how to proceed with the treatment.

5.3 Agent Administration

Trial treatment should be administered after all procedures/assessments have been completed as detailed on the Study Calendar (Section 10.0).

5.3.1 Pre-Surgery Dose Administration

VB-111/placebo must be administrated within 5 days from randomization.

Group A: Participants will receive VB-111 $1x10^{13}$ VPs by intravenous infusion 21±7 days prior to scheduled surgical resection.
Group B: Participants will receive placebo by intravenous infusion 21±7 days prior to scheduled surgical resection.
Group C: Participants will receive placebo by intravenous infusion 21±7 days prior to scheduled surgical resection.

5.3.2 Post-Surgery Dose Administration

For Group A and Group B, upon recovery from surgery (within 28-35 days after surgery), trial treatment should be administered after all procedures/assessments have been completed and reviewed as detailed on the Study Calendar (Section 10). Trial treatment may be administered up to 3 days before or after the scheduled infusion/injection day of each cycle due to administrative reasons.

All trial treatments should be administered on an outpatient basis. If the treating team would like to pursue treatment while inpatient, please contact the Overall Principal Investigator, Dr. Patrick Wen, for prospective approval.

Group A: Participants will resume VB-111 every 6 weeks
Group B: Participants will receive VB-111 every 6 weeks
Group C: Participants will receive standard of care treatments

5.4 Trial Blinding/Masking

Pre-operative treatment will be blinded; therefore, the treating investigator and subject will not know whether VB-111 or placebo is administered. An unblinded pharmacist or designee not involved in other study assessments will prepare the Pre-operative study drug of VB-111/Placebo. Post-operatively, treatment will be unblinded.

5.5 Stratification

Randomization will be stratified according to baseline tumor size (≤15 cc, >15 cc).

5.6 Participant Evaluability

If pre-operative VB-111/placebo is not able to be given to a participant or a participant did not undergo the scheduled surgical resection for any reason, then the participant will be unevaluable for the primary efficacy analysis. Additional patients will be recruited to the trail until 15 evaluable patients in each arm.

5.7 General Concomitant Medication and Supportive Care Guidelines

Therapies, medications or vaccinations specifically prohibited in the exclusion criteria (Section 3.2) are not allowed during the ongoing trial except as outlined below. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Overall Principle Investigator, Dr. Patrick Wen, or his designee. The final decision on any supportive therapy or vaccination rests with the Overall Principle Investigator.

5.7.1 Acceptable Concomitant Medications

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

All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF, when information is available.

All concomitant medications received from date of consent up to 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs.

5.7.2 VB-111 Prophylactic Requirements

To avoid fever following study drug VB-111 administration, all patients will receive 900-1000 mg of acetaminophen starting approximately 1-2 hours prior to VB-111/Placebo dosing followed by 450-500 mg when necessary for up to approximately 36 hours. Prophylaxis of Dexamethasone 4 mg before VB-111/Placebo dosing followed by 4 mg for 3 days may be given if deemed necessary by the investigator.

5.7.3 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy (bevacizumab or biosimilar can be used to control effects of edema and mass effect. A washout period of 2 weeks between each VB-111 and bevacizumab or biosimilar dose is recommended)
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than VB-111
- Radiation therapy
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology or to control cerebral edema. The use of physiologic doses of corticosteroids may be approved after consultation with the Overall Principal Investigator.

Participants who, in the assessment by the treating investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the treating investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial unless otherwise described (e.g. bevacizumab or biosimilar and Group C study treatment). There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7.4 Tumor Treating Fields (TTF)

TFF should not be given from randomization until surgery and after surgery only in Group C. TTF should not be given at any point for Group A and Group B after randomization.

5.7.5 Cerebral Edema

Due to the immunologic nature of VB-111, cerebral edema may theoretically result due to immune infiltration of the brain. Symptoms related to cerebral edema may include headache or neurologic deficit that is either new or worsened. Participants with any signs or symptoms of cerebral edema should be treated as clinically appropriate, including initiation or increased systemic corticosteroid dosing, initiation of bevacizumab or biosimilar, treatment with an osmotic diuretic, or surgical decompression.

Bevacizumab or biosimilar may be used to control edema, mass effect, or as a steroid-sparing agent for as long as the treating investigator deems clinically necessary. Treatment with additional VB-111 may be re-initiated if clinically significant symptoms attributable to cerebral edema have resolved to grade ≤ 1 or pre-treatment baseline or after discussion with the Overall Principal Investigator. A washout period of 2 weeks between VB-111 and bevacizumab or biosimilar doses is recommended. Participants who develop CTCAE 5.0 grade 4 cerebral edema attributable to VB-111 should not receive further doses and should discontinue study therapy.

5.7.6 Diet/Activity/Other Considerations

5.7.6.1 Diet

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

5.7.6.2 Contraception

Eligible female patients will be informed of special restrictions with regards to pregnancy and breast-feeding throughout the study period. Both men and women should not attempt pregnancy and women should not be pregnant or breast-feeding while participating in this study. If sexually active, women of childbearing potential and men with female spouses of childbearing potential must agree to use two methods of reliable contraception simultaneously or to practice complete abstinence from heterosexual contact. One method must include a highly effective method such as an intrauterine device, hormonal (birth control pills, injections or implants), tubal ligation or partner's vasectomy and one can be an additional (barrier method such as a male condom, diaphragm or cervical cap or hormonal) prior to study entry, while receiving treatment and for 120 after undergoing treatment. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.7.6.3 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with the study agent in this clinical trial, the participant will immediately be removed from the study. The site will contact the Overall Principal Investigator and VBL within 1 working day of investigator learning of the pregnancy. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Overall Principal Investigator and to VBL without delay and within 1 working day if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

1. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Overall Principal Investigator and VBL. If a male participant impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Overall Principal Investigator and VBL. Scan and email documents to NeuroOnc_SAE@dfci.harvard.edu and vblsafety@vblrx.com with the subject title as "VB-111 Pregnancy."

5.7.6.4 Use in Nursing Women

It is unknown whether VB-111 is excreted in human milk. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

5.8 Duration of Therapy and Criteria for Removal from Study Treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Treatment may continue for up to 24 months or until one of the following criteria applies:

- The participant or legal representative (such as a parent or legal guardian) withdraws consent
- Radiographic tumor progression is supported by two consecutive time points of tumor growth
  Note: *For unconfirmed radiographic disease progression, please see Section 10.4*

Note: *A participant may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 10.4.*

- Unacceptable adverse event(s)
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the participant
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating Investigator
- Administrative reasons.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy and the date the participant was removed must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

In the event of unusual or life-threatening complications, treating Investigators must immediately notify the Overall Principal Investigator.

5.9 End of Treatment Evaluation and Follow-Up

The End of Treatment and Follow-up visit procedures are listed in Section 10 (Study Calendar). After the end of treatment, each participant will be followed for 30 days for adverse event monitoring and 90 days for SAE monitoring.

Participants removed from protocol therapy for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Participants who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, withdrawing consent or becoming lost to follow-up.

5.10 Long-Term Follow-Up and Study Completion

After documented disease second progression, each participant will be followed by telephone or medical record review for overall survival until they meet criteria for removal from study as detailed below.

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101. Lastly, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

5.11 Participant Replacement Strategy

Additional participants may be enrolled in a given Group to ensure that the required number of evaluable participants in each cohort is achieved. A participant that discontinues the trial for progressive disease or a drug-related AE will be counted in the intention to treat (ITT) population, defined as all randomized participants, but not be evaluable for the primary efficacy analysis in FAS population.

6. DOSE DELAY

For patients who experience an adverse event possibly related to VB-111 and are scheduled for a repeat dose, the repeat dose will be delayed until they meet the criteria outlined in Section 5.2. No dose modifications are allowed.

For patients who experience an adverse event related to standard of care and are scheduled for a repeat dose, the repeat dose will be delayed until they meet the criteria outlined in Section 5.2. Dose reductions are permitted for standard of care therapies, at the discretion of the Investigator. We suggest up to two dose-reductions by 20% for each standard of care therapy.

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

7. ADVERSE EVENTS: REGULATORY AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1.1) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below [reported by CTCAE v. 5 System Organ Class (SOC)] and will determine whether dose delays will be made or whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1 Adverse Event List for VB-111

To date approximately 180 cancer patients were exposed to VB-111 in 4 completed open-label Phase I and II clinical trials. Another 126 patients were exposed to VB-111 treatment in combination with bevacizumab in the completed Phase 3 study in rGBM.

In all VB-111 studies the most frequent adverse events have been constitutional symptoms: fever, chills, fatigue, nausea and headache.

Pyrexia and chills have been often considered related to study medication. They usually occur on the day of study treatment (often 6 hours post-infusion), are transient, and resolve on the same day.

To control these symptoms, all current studies utilize prophylactic as well as post-treatment antipyretic medications. Although transient increases and decreases in blood pressure occurred in a few subjects during the first 24 hours after study treatment, most subjects have remained hemodynamically stable. However, several subjects have been hospitalized with brief hypotension subsequent to dosing with VB-111.

In patients with GBM, symptoms of the underlying brain tumor, such as seizures, confusion/mental changes, gait disturbance/lower extremity weakness, hemiparesis, falls, and speech disorders, such as aphasia/dysphasia/dysphonia have been observed. Some GBM subjects with pyrexia post-VB-111 treatment have developed seizures requiring hospitalization.

The following is a list of adverse events that have been noted most frequently in clinical trials with VB-111:

Most common- incidence higher than 20%
Fever, chills, fatigue, nausea, headache

Very common- incidence between 10 – 20%
Vomiting, diarrhea, constipation, muscular weakness, aphasia, confusional state, dyspnea, hypertension, disease progression

Common with incidence between 5- 10%
Anemia, thrombocytopenia, tachycardia, asthenia, influenza like illness, edema, gait disturbance, fall, urinary tract infection, ALT increase, AST increase, PTT increase, platelet decrease, decreased appetite, hyperglycemia, hypokalemia, hyponatremia, pain, abdominal pain, arthralgia, back pain, dizziness, hemiparesis, seizure, insomnia, hypotension, dysphonia, cough.

Uncommon with incidence less than 1%
Cerebral hemorrhage, brain edema, syncope, infusion related reaction, wound dehiscence, thrombosis, myalgia, muscle spasms, musculoskeletal pain, epistaxis, pulmonary hemorrhage, pleural effusion, cardiac failure, myocardial infarction, intestinal perforation, enterovesical fistula.

For complete safety information refer to the Investigator Brochure.

7.2 Adverse Event Characteristics and Definitions

- Adverse Event (AE) Definition: Any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.
- Serious Adverse Event Definition: Any untoward medical occurrence that fulfills the above definition for an AE and, in addition, at any dose results in any of the following outcomes:
  - Death
  - Is life-threatening

- Persistent or significant disability/incapacity
- Inpatient hospitalization (>24 hour admittance) or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- Any other important medical event that may not be immediately life threatening or result in death or hospitalization but from medical and scientific judgement may jeopardize the participant or require intervention to prevent one or other of the outcomes listed above. These events should usually be considered serious

Note: "life threatening" refers to any adverse experience in which the participant is at immediate risk of death from the reaction at the time of the adverse event; it does not refer to a reaction that hypothetically may have caused death if it were more severe.

Hospitalizations which are for observation or for less than 24 hours are not to be reported as SAEs.

- **The following three point rating scale will be used by the Investigator to rate the maximum intensity of each adverse event:**
  1. Mild: Awareness of signs or symptoms, but no disruption of usual activity.
  2. Moderate: Event sufficient to affect usual activity (disturbing).
  3. Severe: Inability to work or perform usual activities (unacceptable).

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section.

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

7.3 Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

Investigators must report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

Additional Study-Specific Reporting: In addition to events meeting the above criteria, sites will report to Dr. Wen and the DFCI Coordinating Center any wound-related issues >/= gr3, regardless of event seriousness and/or expectedness.

7.3.1 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Table 2: Requirements and Timeline for Reportable AEs.

Adverse Event Characteristics				Notification Requirement		
Serious-ness	**Toxicity Details**	**Known correlation**	**Attribution to study drug(s)**	**Dr. Wen, MD** (Sponsor and OPI) **& DFCI Coordinating Center**	**VBL Safety**	**IRB Submissions**
				Via Email [b], with Safety Reporting Coversheet [c] & MedWatch 3500A [d]		
Serious	Any (incl any Grade 5)	Any (Expected or Unexpected)	Any	Within 1 day from notification [a]	Within 1 day from notification [a]	**All Local IRBs** (including IRB Sub for DF/HCC Sites) To be submitted to local IRB by Site Investigator Team if event meets local IRB submission requirements. To be submitted within IRB established reporting timelines. For DF/HCC sites, please ensure that Dr. Wen (or representative) prospectively approves all submissions. **DF/HCC IRB** DFCI Coordinating Center will be responsible for submitting events from non-DF/HCC sites to DF/HCC IRB per DF/HCC reporting requirements.
Non-Serious	Any Wound-Related Issues >/= Grade 3	Any (Expected or Unexpected)	Any	Within 2 business days from notification [a]	N/A; Not required	
	Grade 4	Unexpected	Any	Within 5 calendar days from notification		
	Grade 2 or 3; moderate or severe	Unexpected	Possible, probable, definite	Within 5 calendar days from notification		

a. For participants enrolled and actively participating in the study or for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.

b. Email the Medwatch 3500A form, coversheet, and the IRB SAE report to the DFCI Coordinating Site with the subject title as "19-792: VB-111 SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to Dr. Wen (the study's Overall Principal Investigator and sponsor/IND-holder), and to Coordinating Center personnel.

c. Safety Reporting Coversheet is found in Appendix C. Coversheet contains all applicable destinations (emails).

d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.2 Protocol-Specific Adverse Event Reporting Exclusions

Events not considered to be serious adverse events in this trial are:

- Hospitalizations which are considered for observation or for less than 24 hours are not to be reported as SAEs.
- Planned surgeries which require an overnight hospital stay are not to be reported as SAEs but should be reviewed with VBL before the surgery.
- An event which is part of the natural course of the disease under study (i.e., disease progression, hospitalization or death due to disease progression) does not need to be reported as an SAE.

7.4 Abnormal Laboratory Values

Laboratory samples drawn in response to a clinically significant value and reported as an adverse event will be documented as unscheduled laboratory evaluations. The tests will be followed-up until the values have returned to within normal range and/or an adequate explanation of the abnormality is established. Should any of these results require confirmation, re-testing will be performed.

7.5 Procedures and Timeline for Reporting of Serious and/or Unexpected Adverse Events

All adverse events encountered from the initial dose of study treatment (including those expected as an outcome of the infusion, i.e. pain at the site of administration) in any study participant during the study will be recorded in detail and indicated on the CRF, regardless of the Investigator's assessment of their relationship to the test drug.

It is the responsibility of the Investigator to ensure that all adverse events which occur during the study are recorded on the CRF. All adverse events occurring after the participant enters the study until 30 days following the last infusion must be reported. Related adverse events will be followed through resolution. Unrelated adverse events will be followed through resolution or end of study.

Safety reporting will be in accordance with 21CFR312.32.

The study period during which all SAEs must be reported begins after the initial dose of study treatment and ends 90 days following the final administration of study drug. SAEs that are observed or reported prior to initiation of the study treatment should be recorded as SAEs on the CRF if they are associated with protocol-mandated interventions (e.g. invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs and SAEs will be recorded on the appropriate eCRF and reported to the DFCI Neuro Oncology Coordinating Center/Overall Principal Investigator in accordance with the protocol. All SAEs should be reported to VBL at vblsafety@vblrx.com.

To report AEs to the DFCI Coordinating Center:

1. Document/describe AE on each of the following:
    a. MedWatch 3500A
        i. Downloadable form at http://www.fda.gov/medwatch/getforms.htm

   b. DFCI Coordinating Center Reportable AE Coversheet
      i. AE Coversheet is found in Appendix C. A modifiable Microsoft Word document is also available from the DFCI Coordinating Center.
2. Scan and email above documents to NeuroOnc_SAE@dfci.harvard.edu with the subject title as "VB-111 SAE"
   a. All AE reports received at this account are forwarded immediately to the Overall PI (Dr. Patrick Wen), and to DFCI Coordinating Center personnel
   b. If available and applicable, please also include the local IRB submission for this event in the submission to the DFCI Coordinating Center.
3. For SAES only scan and email above documents to vblsafety@vblrx.com.

7.6 Handling of Serious Adverse Events

Adverse events classified as "serious" must be recorded on the AE page of the CRF and require expeditious handling and reporting to comply with regulatory requirements. These SAEs will include deaths, regardless of their causal relationship to investigational product. All AEs and SAEs will be reported from the initial dose of study treatment to 30 days and 90 days following the final dose, respectively. Disease progression events will not be reported as SAEs.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries, additional lab and test results, autopsy reports, etc.) should be subsequently collected, if not available at the time of the initial report, and immediately sent to the Sponsor or designee and VBL using the same procedure as the initial SAE report.

For AEs whose toxicity grading is not contained within the CTCAE toxicity criteria, the treating Investigator will be responsible for assessing severity based on the intensity of the event as it presented. Severity will be graded as mild (grade 1), moderate (grade 2), severe (grade 3), or very severe (life threatening – grade 4). The Sponsor recommends that Investigators and study site personnel enter the adverse event term on the CRF and SAE form as accurately as possible, regardless of the CTCAE terminology for the event. The CTCAE should only be used to assign the intensity/severity of the event as described above.

As required, all investigators will be notified of all AE reports that are determined to be serious, unexpected, and related (by the Sponsor) to the investigational product. The notification will be in the form of a Safety Update (Dear Doctor Letter) sent by DFCI.

The notification is considered an addendum to the current Investigator's Brochure; therefore, upon receiving such notices, the Investigator must review and immediately submit a copy to the IRB/approving Ethics Committee (aEC) according to local regulations. The notification must be retained within the Investigator's Brochure. The Investigator and IRB/aEC will determine if the informed consent requires revision. The Investigator also should comply with the IRB/aEC procedures for reporting any other safety information.

In addition to the AE reports that are determined to be serious, unexpected, and related (by the Sponsor) to the investigational product, the DFCI Coordinating Center will also plan circulate to Investigators any reports received of wound-related issues >/= gr3, regardless of event seriousness and/or expectedness for consideration within 5 business days of receipt of the event submission.

7.7 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.8 Reporting to the NIH Office of Biotechnology Activities (OBA)

The Overall PI, as study sponsor, will be responsible for all communications with the OBA. The Overall PI will report to the OBA, regardless of the site of occurrence, any serious adverse event that meets the OBA's criteria for expedited reporting following the reporting requirements and timelines set by the OBA.

7.9 Reporting to the Institutional Biosafety Committee (IBC)

Participating investigators will register and report on research protocols involving biohazards (i.e., recombinant DNA or infectious agents) according to the reporting requirements set by their respective IBC.

7.10 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.11 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. INVESTIGATIONAL AGENT INFORMATION

8.1 VB-111

8.1.1 Description

See Section 2.2.

8.1.2 Form

VB-111 is formulated as a sterile vector solution. The solution is supplied frozen (below -65°C), in single use, 10 ml glass vials. Each vial contains 5mL of vector at a viral titer of 10^{12} VP/ml and vehicle (10% glycerol in Phosphate Buffered Saline). The vector solution should be thawed at room temperature or by rubbing of vial between gloved hands. After thawing, the drug should be diluted as soon as possible in room temperature saline and maintained at this temperature until administration. Note that if needed, the drug may be maintained on ice for up to 3 hours before the dilution. The maximum time for the drug in saline is 60 minutes (+30 minute window) until the end of infusion at room temperature.

8.1.3 Stability and Storage

VB-111 has a shelf-life of 48 months stored at or below -65°C. Open and/or diluted vials should not be re-used.

8.1.4 Compatibility

VB-111 is mixed 1:4 with room temperature saline. Stability of 90 minutes has been established.

8.1.5 Handling and Recommended Precaution Information

- Work Area: Biosafety cabinet level II
- Protective Clothing: Laboratory coat, gloves
- Storage: Borosilicate glass vials that are appropriately labeled, stored at ≤-65°C
- Transport Information: Material should be transported in dry ice
- Spills: Please refer to the MSDS

8.1.6 Packaging and Labeling

VB-111 is packaged in borosilicate vials. Vials are packaged in a storage container labelled with a study identifier, batch number, expiration date, and marked according to local regulatory requirements.

8.1.7 Availability

VB-111 will be distributed to the different sites by a USA depot (PCI). VBL will provide VB-111 to PCI.

8.1.8 VB-111 Preparation

All patients will receive VB-111 in a concentration of $1x10^{12}$ VP/ml diluted in saline (10ml of VB-111 in 40ml Saline). Drug will be administered intravenously every 6 weeks. VB-111 should be prepared and administered as follows: The total dose for patients who weigh >50kg is $1x10^{13}$ VPs administered in 50mL. 2 vials of 5mL of VB-111 ($1x10^{13}$) should be combined with 40 mL of saline to make a total volume of 50 mL. The total dose for patients who weigh less than 50kg is $1x10^{13}$will receive a total dose of $0.7x10^{13}$ VPs administered in 35mL. See Table 3 below for VB-111 preparation:Table 3: VB-111 Preparation.

Patient Weight	Dose (VPs)	Concentration. in vial (VP/ml)	Vol. of VB-111 in vial	# Vials of VB-111	vol. of VB-111 (ml) for 1 dose	Syringe type for VB-111*** *	Vol. of saline	Syringe type for saline	Total vol.	Vol. to inject
≥50Kg	$1x10^{13}$	10^{12}	5ml	2	10 ml	10ml	40ml	60ml*	50ml	50ml
<50Kg	$0.7x10^{13}$ ***	10^{12}	5 ml	2	7 ml	10ml	28ml	60ml**	35ml	35ml

* Prepare the dilution in a saline bag or a syringe
** Use syringe for preparation
***35ml for patients <50kg represents a 30% reduction of VB-111.
**** Needle ≥21G

As VB-111 is included in risk group 2, all work should be done in BSL II conditions. The entire process of drug preparation shall be carried out at room temperature in a biosafety cabinet (BSC). After thawing, the drug should be diluted in room temperature saline, as soon as possible.

Note that if needed, the drug may be maintained on ice for up to 3 hours before the dilution. Once the drug is in its final formulation in saline, keep at room temperature until administration. The maximum time for VB-111/placebo in saline (until completion of administration) is 60 minutes (plus a 30-minute window) at room temperature

The site member preparing the drug shall verify that the information on the container is appropriate for the study and for the participant: product name, concentration, batch number..

- Determine the volume to be applied according to the patient's weight (see Table 1)
- For patients who weigh >50kg: Place 40ml saline (brought to room temperature) in a 60ml sterile syringe. Alternatively, select a 50ml saline bag and remove the dose volume (10ml) and the manufacturer's overfill volume for a total final volume of 50ml.
- For patients who weigh <50kg: Place 28ml saline (brought to room temperature) in a 60ml sterile syringe.
- Thaw two vials of VB-111 solution at room temperature. Rubbing between gloved hands may be used to shorten the process. Be sure to mark the time of thaw.
- For patients who weigh >50kg: Using a 10ml syringe, pull 5ml of VB-111 from each of the vials intended for the specific patient. For patients who weigh <50kg pull 5ml from the first vial and only 2ml from the second vial. Add VB-111 to the syringe/saline bag containing the saline solution prepared in advance. Draw the piston to mix the remaining VB-111 in the syringe with saline and push it back into the syringe/saline bag.
- Mix the diluted drug by swirling the contents by hand.
- Any standard closed system drug-transfer device (CSTD) may be used for drug preparation and administration.
- Place label on the infusion bag/ biuret/syringe. Expiration time must be written.
- After preparation of the drug solution, clean the drug formulation area in the pharmacy using aseptic solution such as 0.9% Virkon, Cavicide, 5.25% Sodium Hypochloride (bleach diluted 1:10), or 70% Ethanol – and leave for at least 10 minutes.
- After completing the preparation, perform a reconciliation process:
  -Check that the correct number of source vials was used.
  -Record vials assigned to the patient in the drug accountability log and in the patient dispensing log.

After preparation of the drug solution, clean the drug formulation area in the pharmacy according to the pharmacy procedures and MSDS. Remaining material used for clinical purposes is collected in their original container and disposed as detailed under the MSDS.
The preparation of the Neoadjuvant dose of VB-111/placebo will be performed by an unblinded site pharmacist or designee who is not involved in other study activities.

Participants who weigh less than 50kg will receive VB-111/placebo at a reduced dose of $0.7x10^{13}$ VPs in 35mL instead of $1x10^{13}$ VPs in 50mL. VB-111 should be prepared and administered as follows: 2 vials of VB-111 should be thawed. 7mL of VB-111 should be taken from the vials (5ml from the first vial and 2ml from the second vial) and combined with 28 mL of saline to make a total volume of 35 mL. Total dose of $0.7x10^{13}$ represents a 30% reduction of VB-111 dose.

8.1.9 Placebo

Normal Saline (NS) will be used as placebo in this study. NS will be provided by the study site.

Placebo should be kept at room temperature until administration**.** The following steps should be followed:

- Determine the volume to be applied according to the participant's weight (see Table 3).
- For patients who weigh >50kg: Place 50ml of saline (brought to room temperature) in a 60ml sterile syringe or select a 50ml saline bag.
- For patients who weigh <50kg: Place 35 ml of saline (brought to room temperature) in a 60ml sterile syringe
- After completing the preparation, record medication assigned to the participant in the participant dispensing log.

Placebo will be administered to participants assigned to Group B and Group C 21±7 days prior to surgery.

Both placebo and VB-111 infusion solutions are clear solutions that are visually indistinguishable. A dispensing log will be kept by the investigational pharmacist or designee, in which he/she will record the date(s) and details of the Placebo dispensed for each participant. The dispensing log will be made available to the study monitor who will verify accountability during the course of the study.

The preparation of the Neoadjuvant dose of VB-111/placebo will be performed by an unblinded site pharmacist or designee who is not involved in other study activities.

8.1.10 Administration

A single intravenous infusion of the diluted VB-111/placebo should be administered at 3mL/minute. An infusion pump or syringe pump may be used.

The maximum time for VB-111/placebo in saline (until completion of administration) is 60 minutes (plus a 30-minute window) at room temperature.

Participants who weigh less than 50kg will receive VB-111/placebo at a reduced dose of $0.7x10^{13}$ VPs in 35mL instead of $1x10^{13}$ VPs in 50mL (refer to Section 8.1.8).

Participants should be observed in the clinic for 60 minutes after each administration of VB-111 or placebo. Monitoring for immediate adverse events should include attention to possible injections site reaction or a systemic reaction. In the absence of the occurrence of an adverse event, participants may be discharged from clinic.

8.1.11 Ordering

Participating institutions will order their own supply of VB-111 directly from the VB-111 drug depot using the Drug Supply Request Form (Appendix D). The first box (3 doses, 6 vials) is to be ordered after the screening and additional supply of a single box (3 doses) should be requested when the local stock is 4 doses (4 vials).

8.1.12 Supplier, Accountability and Return/Destruction of Unused Drug

The investigational center will be supplied with a sufficient quantity of VB-111 to treat participants. The investigational drug will be shipped under appropriate storage conditions to a named unblinded addressee (pharmacist, or other designee, according to the regulations of the investigational center). The drug will be stored at or below -65°C, immediately. Each delivery must be acknowledged by the addressee, or other designee. The pharmacist or his designee will

dispense the drug at the relevant dosing to the investigator.

A dispensing log will be kept by the investigational pharmacist or designee, in which he/she will record the date(s) and quantity of the Investigational Product dispensed for each participant. The inventory documents will be made available to the study monitor who will verify accountability and verify dose during the course of the study. All used and unused containers will be accounted for during the study and will either be returned to the sponsor for destruction or destroyed on site, if approved by the sponsor. A written confirmation of destruction will be delivered.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

We hypothesize that in addition to a direct effect on tumor vasculature, VB-111 may convey a therapeutic effect by inducing an anti-tumor T cell response. The current study will evaluate baseline tumor and peripheral blood (TIL density, TCR clones, immunophenotype, gene expression signatures, and somatic mutation profiles), and changes following VB-111 administration. Additionally, the study will explore the association of biomarkers with outcome.

Tumor samples obtained during the study will be used to evaluate the effect of therapy. Archival tumor expression of TIL density will also be evaluated. If a biopsy or resection is performed at the time of potential progression, a tumor sample should also be submitted if sufficient material is available.

Peripheral blood will be collected prior to initiation of study therapy, prior to surgery and periodically during the study.

Analysis may be extended for additional testing to further elucidate the mechanism of action and to identify subsets of participants likely to respond to VB-111.

9.1 Expanded TCR clones, TIL Density and TCR Overlap

We will evaluate tumor and peripheral blood T cell receptor (TCR) repertoires with next generation sequencing in order to identify expanded and shared TCRs; thereby identifying anti-tumor immune responses induced by VB-111.

Genomic DNA will be isolated from fresh-frozen tumor (protocol surgery) and peripheral blood (immune monitoring time points) and analyzed with next generation sequencing through the TCRVβ region to quantify TIL density and assess the overlap between tumor and peripheral blood.

The number of peripherally expanded TCR clones, TIL density and TCR overlap will then be correlated with clinical variables to identify potential biomarkers with prognostic and predictive value for outcomes (PFS6, OS and toxicity).

TIL density and TCR overlap studies will be performed at Adaptive Biotechnologies (Seattle, WA). Investigators at the UCLA Brain Tumor Immunology Research Laboratory will perform analysis.

9.2 Immunohistochemistry (IHC) Measurements

A minimum of 1 formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) or a minimum of 10 FFPE unstained sections from pre-study surgery confirming GBM are to be submitted. Additionally, a minimum 1 formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) or a minimum of 10 FFPE unstained sections from the protocol surgery are to be submitted per Table 3 below. Archival tumor samples from the protocol surgery should be shipped

to the UCLA Brain Tumor Research Lab. Multi-plex IHC stained will be performed to spatially quantitate PD-1, PD-L1, CD3, CD4, CD8, Iba-1, Ki-67 within the tumor microenvironment by the UCLA Brain Tumor Research Group.

9.3 Immunophenotyping

Tumor and peripheral blood T cell subsets and activation markers will be assessed with mass cytometry high dimensional analysis to identify immune cell subsets that expand or contract in an unbiased fashion during treatment with VB-111. The CD4/CD8 ratio, Treg populations (CD3+,CD4+CD25+CD127low), activation (CD3+CD8+CD25/69), MDSC (CD33+HLA-DrlowCD11b+PD-L1+), negative costimulatory markers (CD3+CD4/8+PD-1+, CD3+CD4/8+CTLA-4+) will be determined at each time point. CyToF analysis will be performed on PBMC obtained from Ficoll density gradient separation of whole blood. Blood draws for this testing will be performed pre-treatment, pre-surgery, and with every MRI scan obtained for tumor status. Guidance on peripheral blood collection, processing and shipping is provided in Table 4 below.

9.4 Cell-Cycle Related Gene Signatures, Gene Expression Signatures and Somatic Mutations

Tumor samples from the protocol surgery should be immersed in Allprotect tissue reagent solution (Qiagen) and taken to the UCLA Brain Tumor Research Laboratory. RNA-seq will be performed at the UCLA GenoSeq Core facility and analyzed. We will assess the number of somatic mutations in each tumor, and data will be correlated with clinical variables to identify potential biomarkers with prognostic and predictive value for outcomes (PFS, OS). We will also explore cell-cycle related gene signatures (Nanostring IO360) and sequencing data to determine whether an existing immune signature correlates with clinical variables.

9.5 Transgene and Viral Analysis

RNA will be extracted from the fresh frozen tissue sample using RNA isolation kits. RNA samples will be tested by QPCR for trans-gene and viral antigen expression in the tissue. This analysis will be performed by VBL.

Table 4: Correlative Sample Summary.

Integral and Integrated Biomarkers:

Biomarker name (Lead PI, Site)	**Assay**	**Tissue/Body Fluid Tested (Timing of Assay)**	**Mandatory /Optional**
Expanded TCR clones (integrated biomarker) (R Prins/T Cloughesy/L Liau, UCLA)	immunoSEQ Assay (Adaptive Biotechnologies) on tumor tissue and PBMC genomic DNA	Tumor (at the time of on study) and peripheral blood (pre-Neo-adjuvant treatment, at the time of surgery, pre-dose on D1 of post-surgery adjuvant treatment cycle 1, and with every MRI during the adjuvant treatment)	Mandatory
TIL Density and TCR Clonality (R Prins/T Cloughesy/L Liau, UCLA)	immunoSEQ Assay (Adaptive Biotechnologies) on tumor tissue and PBMC genomic DNA	Tumor (at the time of on study surgery) and peripheral blood (pre- Neo-adjuvant treatment, at the time of surgery, pre-dose on D1 of post-surgery adjuvant treatment cycle 1, and with every MRI during the adjuvant treatment)	Mandatory

Exploratory Biomarkers Table

Biomarker name (Lead PI, Site)	**Assay**	**Tissue/Body Fluid Tested (Timing of Assay)**	**Mandatory /Optional**
Cell cycle-related gene signature (integrated biomarker) (R Prins/T Cloughesy/L Liau, UCLA)	RNA-seq and Nanostring IO360	Tumor (at the time of on study surgery)	Optional
IHC measurements (R Prins/T Cloughesy/L Liau, UCLA)	PD-1/PD-L1/CD3/CD4/CD8/Iba-1/Ki-67 IHC on FFPE tumor tissue	Tumor 10 unstained slides (archived and protocol surgery)	Optional
Peripheral blood T cell subsets/activation markers (R Prins/T Cloughesy/L Liau, UCLA)	Mass Cytometry on PBMC	Peripheral blood (pre- Neo-adjuvant treatment, at the time of surgery, pre-dose on D1 of post-surgery adjuvant treatment cycle 1, and with every MRI during the adjuvant treatment)	Optional
Gene expression signatures and somatic mutations (R Prins/T Cloughesy/L Liau, UCLA)	RNA Seq on tumor RNA Exome sequencing on normal/tumor gDNA	Tumor (at the time of on study surgery) and peripheral blood (at the time of on study surgery)	Optional

Exploratory Transgene expression Table

Biomarker name (Lead PI, Site)	**Assay**	**Tissue/Body Fluid Tested (Timing of Assay)**	
Cell cycle-related gene signature (integrated biomarker) (R Prins/T Cloughesy/L Liau, UCLA)	PCR and qPCR	Tumor (at the time of on study surgery)	Optional
Transgene and viral RNA	qPCR	Tumor (at the time of on study surgery)	Mandatory

Imaging Correlates Table

Correlative Objective (Lead PI, Site)	**Imaging Technique**	**Organ(s) Scanned (Timing of Scans)**	**Mandatory /Optional**
Accurate distinction between tumor and inflammation (B Ellingson, UCLA)	MRI (ADC, Perfusion)	Brain (pre- Neo-adjuvant treatment, Pre-surgery, post-surgery, every 6 weeks during adjuvant treatment, EOT)	Mandatory

10. STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 28 days of randomization unless indicated otherwise. Assessments must be performed and reviewed prior to administration of any study agent at any treatment visit unless otherwise noted in footnotes below. Study assessments should be performed and study agents should be administered within +3/-3 days of the protocol-specified date, unless otherwise noted.

Assessments	**Screening[1]/ Randomization**	**Neo-Adjuvant** Therapy	**Pre-surgery/ Surgery** [34]	**Post-surgery**	**Pre-Adjuvant Tx cycles** [5]	**Day 1 of each Adjuvant Tx Cycle**	**End of Tx** [7]	**30-Day Post Drug** [8]	**Active Follow Up** [9]	**Long Term Follow Up** [10]	**EDC Timepoints**
Informed Consent [11]	X										Screening
Background Information/History [12]	X										Screening
Inclusion/Exclusion Criteria [13]	X										Screening
Vital Signs [14]	X		X		X		X				Screening, Pre-surgery, Pre-Adjuvant, End of Tx
Neurologic Exam [15]	X					X	X				Screening, Day 1 each adjuvant cycle, End of Tx
Directed Physical Exam [16]	X		X			X	X				Screening, Pre-surgery, Day 1 each adjuvant cycle, End of Treatment
Karnofsky Performance Status [17]	X		X		X		X	X			Screening, Pre-surgery, Pre-adjuvant treatment, End of Treatment, 30-Day Post Drug
Concomitant Medications [18]	X		----------X----------								Screening, through trial duration up to 30day post Drug
Adverse Event Assessment [19]			----------X----------								Pre-surgery, through trial duration up to Long Term Follow-up
Pregnancy Test [20]	X				X		X				Screening, Pre-Adjuvant treatment, end of Tx
Coagulation [21]	X		X								Screening
Hematology [22]	X	X[2]	X[4]		X		X				Screening, Neo Adjuvant Treatment, Pre-surgery, Pre-Adjuvant Cycles, End of Tx
Serum Chemistry [23]	X	X[2]	X[4]		X		X				
Virology [24]	X										Screening
Imaging – MRI [25]	X		X	X	X[26,32]		X[32]		X[32]		Screening, Pre-surgery, Post-Surgery, Pre-Adjuvant Cycles, End of Tx, Active Follow-up
Response Assessment [26]					X		X		X		Pre-Adjuvant Cycles, End of Tx, Active Follow-up
VB-111 administration [27]		X[3]				X[6]					Neo Adjuvant Treatment, Day 1 each adjuvant cycle.
Placebo administration [27]		X[3]									Neo Adjuvant Treatment.
Research blood[28]		X[33]	X		X		X				Screening, Pre-surgery, Pre-Adjuvant Cycles, End of Tx
Archival Tissue and surgical tissue [29]			X								Surgery
Post-EOT Therapies [30]								X	X	X	30 day Post Drug, Active Follow-up, Long Term Follow-up
Survival [31]									X	X	Active Follow-up, Long Term Follow-up

1. All screening procedures to be performed within 14 days of randomization, except for informed consent, virology testing, and pregnancy test. Virology testing may occur up to 6 months prior to randomization (see footnote 24); Informed consent may occur up to 28 days prior to randomization (see footnote 11); and Pregnancy test for women of childbearing potential must be done within 72 hours prior to registration (see footnote 20).
2. Repeat laboratory testing if >3 days from screening laboratory evaluations.
3. Neo-adjuvant treatment with VB-111/Placebo must be initiated within 5 days of Randomization.
4. Screening assessments may serve as pre-surgery treatment assessment if < 14 days from the screening, except in the event that there are any indications that the participant's condition is deteriorating, for which laboratory evaluations should be repeated on the day of initiation of pre-surgery treatment. If > 14 days from screening assessment, laboratory evaluations should be repeated on the day of initiation of pre-surgery treatment.
5. For all post-surgery cycles, required assessments should be performed within 3 days of scheduled visit days.
6. Post-surgery window requirements: VB-111 must be administered 28-35 days from surgery. Assessments must be performed and reviewed prior to study agent administration.
7. End of treatment assessments to be performed within 7 days after last drug administration or within 7 days after decision to end treatment. Assessments may continue for ongoing reportable adverse events. Do not repeat the safety laboratory tests and physician exam if the previous assessments were completed within 14 days from the EOT visit.
8. A contact/visit is to be performed at 30 days (+7 days) after the last study drug is given. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last study drug.
9. For participants who discontinue study treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging at a schedule developed by the treating investigator until (1) documented disease progression, (2) death or (3) the end of the study, whichever occurs first.
10. Long Term Follow Up: participants will be followed every 3 months (+/- 1 month) via contact or medical record review until death for post-treatment therapies, reason for stopping those therapies and survival.
11. Informed Consent must be obtained by a delegated MD attending. No study specific screening procedures may occur until after the informed consent process is complete. Informed Consent may be obtained within 28 days of enrollment.
12. Background information/history is to include review of treatment history for GBM, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
13. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant meets all eligibility criteria must be available prior to registration.
14. Vital signs include weight, heart rate, blood pressure, respiration rate, temperature. Vital signs must be performed prior to administration of treatment on treatment days. Height required only at screening.
15. Neurologic Exam is to be completed by the investigator or qualified designee at screening, and Day 1 of post-surgery treatment cycles.
16. Directed Physical Exam is to be completed at screening, pre-surgery treatment visit, Day 1 of post-surgery treatment cycles, and as clinically indicated by the investigator or qualified designee.
17. Performance Status is to be assessed by KPS (Appendix A).
18. Concomitant medications and reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs.
19. Adverse events experienced by participants will be collected and recorded from the first dose of study treatment up to the 30-Day Post Drug Visit of the last dose of study medication (+ 7 days depending on when 30-Day Post Drug visit/contact occurs) and all SAEs (related and unrelated to trial treatment) up to 90 days after the last dose of treatment. Afterwards, report only SAEs that are considered related to trial treatment. Adverse events may also occur in screened participants during pre-allocation baseline period as a result of a protocol-specific intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.
20. For women of child bearing potential, a urine pregnancy test must be performed. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
21. PT/INR, PT, PTT are required at screening and PTT will be checked again with pre-surgery labs. Thereafter,

coagulation to be checked when clinically indicated.

22. Hematology includes erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
23. Serum Chemistry includes albumin, alkaline phosphatase (ALP), bicarbonate (HCO_3), BUN, calcium, chloride, creatinine, glucose, magnesium, potassium, SGOT (AST), SGPT (ALT), sodium, total protein, total bilirubin.
24. Virology panel includes Hepatitis A Antibody, Hepatitis B Core IgG and M Antibody (Anti-HBC, total), Hepatitis B Surface Antibody (Anti-HBs), Hepatitis B Surface Antigen (HBsAg), Hepatitis C Surface Antibody (anti-HCV), HIV-1/2 Ag/Ab and HTLV-1/2 Ag/Ab. If any hepatitis serology is positive, qualitative PCR for Hepatitis B DNA or Hepatitis C RNA will be obtained and results must be negative for eligibility.
25. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 14 days prior to enrollment. On-study imaging should be performed every 6 weeks starting from post-surgery treatment Cycle 1 Day 1. The same imaging technique should be used in a participant throughout the trial, if feasible. Local reading (investigator assessment) will be used to determine eligibility and for participant management.
26. Response Assessment to be completed per RANO criteria (Section 10).
27. Pre-surgery VB-111/placebo administration is required for participants in all Groups 21±7 days prior to surgery. Group A and B will receive post-surgery VB-111 administration and it must start 28-35 days after surgery. Post-surgery VB-111 may be administered ±3 days from day 1 of each cycle. To avoid fever following study drug VB-111 administration, all patients will receive 1) 900-1000 mg of acetaminophen starting 1-2 hours prior to VB-111/Placebo dosing followed by 450-500 mg when necessary for up to 36 hours and 2) dexamethasone 4 mg 1-2 hours prior to VB-111/Placebo dosing followed by 4 mg for 3 days may be given if deemed necessary by the investigator.
28. Blood for biomarker evaluation: please see Table 4 Correlative Sample Summary for details on collection requirements.
29. Pre-study archival tumor tissue is to be submitted within 60 days of Randomization. Protocol surgery tissue is to be collected during the trial. Please see Table 4 Correlative Sample Summary for details on collection requirements.
30. Start/stop dates, names of treatment regimens and reason for stopping should be collected.
31. Date of death and reason should be collected for overall survival purposes, when applicable.
32. For all participants, if the post-surgery MRI is greater than 21 days from post-surgery VB-111 then MRI must be repeated on Cycle 1 Day 1. Starting from EOT visit, the participants will be followed up by radiologic imaging per standard of care.
33. The baseline research sample at the neoadjuvant time point must be drawn before treatment begins.
34. The Pre-Surgical Visit / Assessments will be done either on day of surgery or within 3 days prior to surgery.

11. MEASUREMENT OF EFFECT

Tumor response will be assessed every 6 weeks using contrast and non-contrast brain magnetic resonance imaging (MRI) with assessment based on the RANO criteria [55] until progression is supported by two consecutive time points of tumor growth (local and central blinded independent radiology review). For participants who do not progress or die, PFS will be censored at the last adequate radiologic assessment. Baseline scan for determining progression will be the post-operative scan obtained just prior to initiating post-operative therapy.

Clinicians may repeat response assessment more frequently as clinically indicated.

11.1 Anti-Tumor Effect Definitions

11.1.1 Evaluable for Toxicity

All participants who receive at least one dose of VB-111/placebo will be evaluable for toxicity from the time of their first treatment.

11.1.2 Measurable Disease

Measurable disease is defined as bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI, with two perpendicular diameters of at least 10mm, visible on 2 or more axial slices which are preferably at most 5mm apart with 0mm skip. The presence of inter-slice gaps should be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity should be considered non-measurable unless there is a nodular component measuring at least 10mm in diameter. The cystic or surgical cavity should not be measured in determining response.

All tumor measurements must be recorded in millimeters.

11.1.3 Non-Measurable Disease

Non-measurable disease is defined as either uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameter <10mm.

11.1.4 Target Lesions

All measurable lesions up to a maximum of 5 lesions should be identified as target lesions and recorded and measured (sum of the products of the perpendicular diameters) at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repeated measurements by imaging techniques. Occasionally, the largest lesions may not be suitable for reproducible measurement and the next largest lesions which can be measured reproducibly should be selected.

11.1.5 Non-Target Lesions

For participants with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered non-target lesions and should also be recorded.

Rarely, unequivocal progression of a non-target lesion requiring discontinuation of therapy, or development of a new contrast-enhancing lesion may occur even in the setting of stable disease (SD) or partial response (PR) in the target lesions. These changes would qualify as progression.

Non-target lesions also include measurable lesions that exceed the maximum number of 5.

Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

11.1.6 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed up to 28 days before the beginning of the treatment.

Conventional MRI is required, CT is not acceptable. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. These techniques should be performed with contiguous cuts of 10mm or less in slice thickness. The MRIs will be evaluated both locally and centrally by a core lab.

11.2 Response Criteria for Target Lesions

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

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
b) No new lesions
c) Stable or improved non-enhancing (T2/FLAIR) lesions
d) Participants must be off corticosteroids
e) Stable or improved clinically

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

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks
b) No progression of non-measurable disease
c) No new lesions
d) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan
e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of the baseline scan
f) Stable or improved clinically

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

a) Does not qualify for CR, PR, or progression
b) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan
c) Stable clinically

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

a) ≥ 25% increase in the sum of products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids
b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects)
c) Any new lesion

d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose
e) Failure to return for evaluation due to death or deteriorating condition
f) Clear progression of non-measurable disease.

The RANO Response Criteria are summarized in Table 5.

Table 5: Summary of RANO Response Criteria.

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease to <25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NA= not applicable
[#] Progression occurs when any of the criteria with * is present
[NA] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

11.3 Confirmatory Measurement/Duration of Response

11.3.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessment that should be performed at least 4 weeks after the criteria for response are first met.

11.3.2 Duration of Overall Response

The duration of overall response is measured from the time criteria are met for CR or PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

11.3.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.4 Modified RANO (iRANO): Study Continuation Beyond Initial Progressive Disease

Immunotherapeutic agents such as VB-111 may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may manifest as initial worsening of enhancement and edema on MRI (i.e. pseudoprogression). In addition, the response patterns seen with immunotherapies may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the

appearance of new lesions. For these reasons, the immune-related response criteria (irRC) have endorsed continuation of study therapy beyond initial radiographic evidence of progression for clinically stable participants undergoing immune based therapies [56].

A major advance of the RANO criteria [55] to assess response in neuro-oncology over the previously used Macdonald criteria [57] includes recognition of the prevalence of pseudoprogression during the first three months following completion of radiation and daily temozolomide [58, 59]. Specifically, RANO permits participants with such progressive MRI findings to continue temozolomide therapy for up to three months in order to avoid inaccurately classifying such participants as progressive. Furthermore, RANO permits participants with progressive radiographic findings to continue current therapy pending follow-up imaging if the etiology of progressive imaging findings is unclear. Standard RANO may not provide an accurate response assessment of immunotherapeutic agents such as VB-111.

Therefore, the following adaptations of the RANO criteria will be used to assess response for participants treated on this study in an exploratory fashion (Table 6):

- Potential Pseudoprogression: If radiologic imaging shows initial PD, participants who are not experiencing significant clinical decline (e.g. significant decrease in KPS), may be allowed to continue study treatment until progression is supported by two consecutive time points of tumor growth. Participants should be closely monitored with MRIs every cycle (approximately every 6 weeks) during this period. Participants who have radiographic evidence of further progression after up to three months, or who decline significantly at any time, will be classified as progressive with the date of disease progression back-dated to the first date that the participant met criteria for progression and such participants will be discontinued from study therapy. Although the kinetics of pseudoprogression due to immune therapy among glioblastoma participants is currently unknown, three months is a reasonable estimate based on: 1) the peak time for XRT/daily temozolomide-related pseudoprogression is usually within three months of completion for glioblastoma participants [56, 57] and; 2) three months is also the most common timeframe for pseudoprogression observed among participants with advanced melanoma or other solid tumors treated with immune therapies such as immune checkpoint blockade to date [60-62].

  Among participants on this study with initial radiographic PD, tumor assessment should be repeated regularly (approximately every 6 weeks) in order to confirm PD with the option of continuing treatment and the addition of bevacizumab or biosimilar while awaiting radiologic confirmation of progression.

  Participants who have progression that is supported by two consecutive time points of tumor growth will discontinue study medication and enter the follow up/survival phase of the study. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

- Tumor Enhancement to Define Progression: RANO expanded the previously utilized Macdonald criteria[73] to include the development of "significantly" increased T2 or FLAIR abnormality in the definition of progressive disease because such changes can be a major component defining radiographic progression following therapeutic use of VEGF/VEGFR-targeting therapeutics which are known to elicit potent anti-permeability changes that limit contrast uptake. However, immune based therapies are expected to be associated with

inflammatory changes that may include edema. Therefore, radiographic progressive disease will be defined by assessment of enhancing tumor and will not declare tumor progression based on the presence of T2 or FLAIR changes alone as outlined in RANO because:

- There is no expectation that immunotherapy agents will falsely diminish enhancing tumor burden as has been noted with anti-angiogenic therapies; and
- Immune based therapies are expected to induce inflammatory responses which may be associated with increased edema and T2/FLAIR changes. Such radiographic finding may inaccurately be interpreted to represent tumor progression (i.e. pseudoprogression).

In participants who have initial evidence of radiographic PD, it is at the discretion of the treating physician whether to continue a participant on study treatment for up to three months pending confirmation of PD on follow-up imaging. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may receive bevacizumab or biosimilar 10mg/kg2 every 2 weeks in addition to study treatment while waiting for confirmation of PD if they are not experiencing significant clinical decline and the participant is adequately tolerating study therapy (if a participant is required to discontinue study treatment for toxicity as defined per protocol section 5, then they must be taken off-treatment).

When feasible, study therapy should not be discontinued until progression is supported by two consecutive time points of tumor growth. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response [49]. Participants that are exhibiting significant neurologic decline are not required to have repeat imaging for confirmation of progressive disease.

Table 6: Imaging and Treatment After 1st Radiographic Evidence of PD.

	No Significant Neurologic Decline		Significant Neurologic Decline	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging (every cycle, approximately every 6 weeks) for up to 3 months to confirm PD	May continue study treatment at the Investigator's discretion for up to 3 months while awaiting confirmatory imaging assessment	Repeat imaging 6 weeks later to confirm PD if possible	May continue study treatment and start bevacizumab or biosimilar 10mg/kg Q2 weeks until the next scheduled imaging assessment. A washout period of 2 weeks between VB-111 and bevacizumab or biosimilar doses is recommended.
Repeat scan up to 3 months after 1st radiologic evidence confirms PD	No additional imaging required; date of tumor progression back-dated to date of initial radiographic PD	Discontinue treatment	No additional imaging required; date of tumor progression back-dated to date of initial radiographic PD	Discontinue treatment
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 6 weeks	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks	May continue study treatment and continue bevacizumab or biosimilar indefinitely. A washout period of 2 weeks between VB-111 and bevacizumab or biosimilar doses is recommended,

A participant may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved. The exception will be granted following discussion with Sponsor and VBL.

Participants with progressive radiographic findings are encouraged to undergo surgical intervention in order to delineate pseudoprogression due to inflammation associated with VB-111 from true tumor progression. Participants with histopathologic findings of significant immune infiltrate and evolving gliosis will be allowed to continue study therapy. In contrast, those with clear evidence of progressive tumor by histopathologic evaluation will be defined as progressive and discontinued from study therapy. For such participants, the date of tumor progression will be the first date the participant met radiographic criteria for PD.

11.5 Radiology Review

The review of the baseline neuroimaging will be performed at DFCIto ensure the participants meet the inclusion criterial before the randomization. The review of on-study neuroimaging will be performed retrospectively at DFCI.

12. DATA REPORTING/REGULATORY REQUIREMENTS

12.1 Data Reporting

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.1 Responsibility for Data Submission

All investigative sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ as noted in Table 7 below.

Table 7: Study Data Submission Table.

Form	Submission Timeline
Eligibility Checklist	Complete prior to study registration
On Study Form	Within 30 days of registration
Baseline Assessment Form	Within 30 days of registration
Treatment Form	Within 30 days of treatment administration
Adverse Event Report Form	Within 30 days of AE assessment/notification
Response Assessment Form	Within 30 days of the response assessment
Off Treatment/Off Study Form	Within 30 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 30 days of the protocol defined follow up visit date or call

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC

Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

13. STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

13.1 Study endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

13.1.1 Efficacy Endpoints

Tumor infiltrating T cell (TIL) density is defined as the number of T lymphocytes per nucleated cell, and calculated by detailed sequencing of recombined T cell receptor sequences obtained from the tumor specimen gDNA.

PFS6 is defined as the percentage of participants with progression-free survival at 6 months from surgery as defined by RANO.

OS is defined as the time from randomization until death from any cause. Participants will be followed for survival status after progression or discontinuation of the study drug for other reasons.

13.1.2 Safety Endpoints

The primary safety endpoints are AEs graded using CTCAE version 5.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by participants who have received VB-111, including serious adverse events (SAEs). Other safety endpoints include laboratory safety assessments, KPS status, vital signs and physical examinations.

13.2 Definitions of Analysis Sets

- The Full Analysis Set (FAS) population will serve as the population for the analysis of primary efficacy endpoint TIL density in this study. The FAS population consists of all participants within each cohort who have received a preoperative dose of VB-111/placebo and had a surgery.
- The intention to treat (ITT) population is defined as all randomized participants. The ITT population will be used for secondary efficacy endpoints (PFS6, OS).
- The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all allocated participants who received at least one dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

13.3 Sample Size Consideration

This is a randomized, controlled, blinded, phase II, surgical trial to evaluate early immunologic pharmacodynamic parameters for the viral cancer therapy VB-111 in participants with surgically accessible recurrent/progressive glioblastoma (rGBM). Participants will be randomly assigned to group A or B or C with a 1:1: 1 randomization ratio prior to surgery. The primary hypothesis is that VB-111 can generate effective anti-tumor immune responses in the form of a statistically significant increase in TIL density comparing Group A (neoadjuvant/adjuvant) vs combined control group (Group B+C).

Based on our preliminary data, the mean of TIL density is estimated to be 0.4 (T cells per nucleated cell) (SD=0.5) in the combined control group (Group B and C). Comparing Group A vs Group B+C at an alpha level of 0.05 (1-sided) using a stratified two-sample t-test, a sample size of 30 in the combined Group (B+C), and 15 in Group A (Total of 45 evaluable) allows for the detection of a standard difference in TIL density of 0.8 or larger with 84% power. Effect size is defined as Cohen's D, the difference of two population means, divided by the pooled standard deviation. [63]

13.4 Efficacy Analysis

A two-sample t-test with tumor size stratification will be used to test the difference of tumor infiltrating T cell density between the two groups (Group A vs combined Group B+C). Data distribution will be examined prior to analysis. Data transformations will be performed as deemed appropriate.

For the secondary endpoint of PFS6, historical comparison data are available from a pooled analysis of Phase II experience in recurrent Grade IV gliomas who have undergone surgery either just prior to starting treatment or as part of the protocol, which documented a PFS6 rate of 10%. Group comparisons (Group A vs C; Group B vs C; Group A+B vs C) will be conducted using the exact binomial test with Bonferroni adjustment to compare PFS6 rate at one sided alpha of 5%.

For OS, analyses will be conducted using historical comparison data which are available from a pooled analysis of Phase II experience in recurrent Grade IV gliomas who have undergone surgery either just prior to starting treatment or as part of. Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Participants without efficacy evaluation data or without survival data will be censored at Day 1. For evaluation of the expansion of TCR clones, a two-sample T-test with Bonferroni adjustment will be used to compare the increase number of expanded TCR clones after VB-111 in Group A+B vs Group C.

13.5 Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Safety summaries will be reported for both cohorts. Death (other than death related to progressive disease) that occurs within 30 days of VB-111 administration will lead to pausing of the study and analysis of the toxicity data.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, and vital sign parameters that are not pre-specified as events of interest will be summarized with descriptive statistics (counts, percentage, mean, standard deviation, etc.).

Continuous measures such as changes from baseline in laboratory, and vital signs parameters that

are not pre-specified as events of interest will be summarized using descriptive statistics (mean, standard deviation, etc.) for baseline, on-treatment, and change from baseline values.

13.6 Exploratory Analyses

Variables involved in exploratory analyses will be examined graphically and summarized by descriptive statistics. Data transformation may be applied to quantitative variables prior to analyses if deemed necessary.

Bivariate association analyses will be conducted to evaluate the associations between exploratory biomarkers and clinical outcomes and adverse events for the objectives listed in 1.4. The analyses will be performed for each group separately and/or combined as deemed appropriate. Specifically, Pearson or Kendall's tau correlation coefficients will be calculated to evaluate the association between quantitative variables, Chi-squared tests or Fisher's exact tests will be used to examine the association between categorical or ordinal variables, and ANOVA will be performed to study the association between a quantitative variable and a categorical variable. The association between biomarkers and clinical outcomes (PFS and OS) will be evaluated using Cox regression and elastic net regularized regression for variable selection. For markers with multiple measurements over time, data at a specific time point or change from pre-treatment will be used in the above bivariate analyses as deemed appropriate.

Changes in markers pre- and post- treatment will be assessed using paired t-tests.

Between-group comparisons will be conducted for PFS, OS, TIL density, interferon and cell cycle-related genetic signatures, and IHC expression. Survival analyses via Kaplan-Meier curves and log-rank tests will be used to estimate and compare PFS, second PFS, and OS between Group A, Group B, and Group C.

13.7 Baseline Characteristics and Demographics

Baseline characteristics will be assessed by the use of tables and/or graphs for each cohort separately. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables

13.8 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the participant receives the study medication/Placebo infusion. The number of Days Should be on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication. For each participant, percent compliance will then be calculated using the following formula:

Percent Compliance = (Number of Days Should be on Therapy/Number of Days on Therapy) x 100

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

13.9 Extent of Exposure

Extent of Exposure for a participant is defined as number of cycles in which the participant receives

the study medication infusion. Summary statistics will be provided on Extent of Exposure for APaT population.

13.10 Procedure for Accounting for Missing, Unused and Spurious Data

Missing data will be indicated in the listings, but excluded from all descriptive analyses. All data will be listed, including otherwise unused data. Spurious data will be identified as such, wherever possible.

14. PUBLICATION PLAN

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor-Investigator will work with the authors and VBL to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last participant visit in some cases. The Overall Principal Investigator will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last participant's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, participant to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol which includes the statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the participant inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. VBL and the Sponsor reserves the right to redact proprietary information.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor-Investigator and VBL must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor or VBL as confidential must

be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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APPENDIX A: KARNOFSKY PERFORMANCE STATUS

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

* Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity and guidelines.J Clin Oncol. 1984;2:187-193.

APPENDIX B: MULTI-CENTER DATA AND SAFETY MONITORING PLAN

DFCI IRB Protocol #: 19-792

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1.0 INTRODUCTION 63
1.1 Purpose 63
1.2 Multi-Center Data and Safety Monitoring Plan Definitions 63

2.0 GENERAL ROLES AND RESPONSIBILITIES 64
2.1 DF/HCC Sponsor 64
2.2 Coordinating Center 65
2.3 Participating Institution 65

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS 66
3.1 Protocol Distribution 66
3.2 Protocol Revisions and Closures 66
3.3 Informed Consent Requirements 67
3.4 IRB Documentation 67
3.5 IRB Re-Approval 67
3.6 Participant Confidentiality and Authorization Statement 68
3.7 DF/HCC Multi-Center Protocol Registration Policy 68
3.8 DF/HCC Protocol Case Number 72
3.9 Protocol Deviations, Exceptions and Violations 72
3.10 Safety Assessments and Toxicity Monitoring 73
3.11 Data Management 74

4.0 REQUISITIONING INVESTIGATIONAL DRUG 75

5.0 MONITORING: QUALITY CONTROL 75
5.1 Ongoing Monitoring of Protocol Compliance 75
5.2 Monitoring Reports 77
5.3 Accrual Monitoring 77

6.0 AUDITING: QUALITY ASSURANCE 77
6.1 DF/HCC Internal Audits 78
6.2 Audit Notification 78
6.3 Audit Reports 78
6.4 Participating Institution Performance 78

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that s/he may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2.0 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Patrick Wen, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable.

- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites, and IBC approval
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.
- Report SUSARs to the FDA and VBL according to the FDA.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the DF/HCC Sponsor/Coordinating Center in accordance with DF/HCC requirements, and to VBL.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor/Coordinating Center in accordance with DF/HCC requirements.
- Order, store, dispense, and destroy investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the

Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.
- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians obtain initial informed consent and any re-consent that requires a full revised consent form.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB
- Participating Institution’s IRB approval for all amendments
- Annual approval letters by the Participating Institution’s IRB

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant-specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

Eligible participants will be entered on study centrally at the DFCI Coordinating Center (by a Coordinating Center specialist, if participant is at a non-DF/HCC site). Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A qualified member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. A Coordinating Center specialist should be notified of cancellations - or any status changes - as soon as possible.

In order to register a participant onto study, the following must be done:

- Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
- Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record.
    - **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

After participant has been registered to study:

1. A separate Multi-Center Coordinating Center specialist (19-792 Unblinded Contact, or back-up) will inform the participating site's pharmacy contact of the successful randomization via Fax or email, to include Applicable treatment arm assignment, and requests a confirmation

2. Site's pharmacy contact confirms receipt of patient's assignment via email to 19-792 Unblinded Contact (or back-up)

3. The Designee (Multi-Center Coordinating Center specialist) emails Site Team to confirm pharmacy contact has received patient's randomization assignment

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered and randomized.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.7.1 Participant Registration and Randomization at a non-DF/HCC Site

To register a participant at any non-DF/HCC site, the subsequent procedure is to be followed:

1. The participating site's data manager/coordinator/research nurse should contact a DFCI Neuro-Oncology Coordinating Center team member via telephone or email to:
    - Notify regarding the pending registration
    - Confirm the methods of sending documents and communication for registration
    - Communicate desired timeline of the registration (i.e. the next day, etc.).

    Multi-Center DFCI Neuro-Oncology Designee contact information:
    E-mail: NeuroOnc_Coor@dfci.harvard.edu
    Phone: 617-582-7101

2. The data manager/coordinator/research nurse should then send the following documents to the Coordinating Center specialist:
    - Completed DF/HCC study specific Eligibility Screening Worksheet
    - Copy of protocol required test results (e.g. coagulation studies, hematology panel, serum pregnancy test, serum chemistry panel, urinalysis -- all as applicable per protocol)
    - Copy of the pathology and surgical reports
    - List of current concomitant medications (obtained within the protocol-specified screening window) including sign/date by RN/other clinician and documentation of when reviewed/confirmed with patient
    - Copy of signed informed consent form
    - Copy of signed HIPAA authorization form (if separate from the informed consent document)
    - Copy of clinic note(s) and other medical records that document consenting process, screening and eligibility, if available***

    Documents will be transmitted via one of the following methods:
    Scanned and emailed to: NeuroOnc_Coor@dfci.harvard.edu or direct email of Coordinating Center specialist
    Faxed to: 617-394-2683

*** *The Coordinating Center Specialists would like to review and monitor participant eligibility, informed consent, screening and baseline assessments on all participants. Providing a complete set of source documents prior to registration may delay registration. Participating Institutions will work with the Coordinating Center Specialists to determine what documents may feasibly be available for review prior to enrollment, and these documents are to be provided for pre-enrollment review. A complete set of documents will be provided to the Coordinating Center after registration; the timeline will be determined by the Coordinating Center Specialist based on the study team's experience with the trial and prior monitoring findings. If there are persistent issues with eligibility at a site or with a study overall, the Coordinating Center may require that all source documentation relevant to participant eligibility be provided prior to proceeding with participant registration.*

3. After having received all transferred documentation, the Designee (Coordinating Center specialist) will review the documents to verify eligibility and notify the participating site of the result.

4. To complete the registration process, the Designee (Multi-Center Coordinating Center specialist) will follow DF/HCC Standard Operating Procedure for Human Participant Research Titled *Participant Protocol Registration* (SOP #: REGIST-101) and register the participant centrally on the protocol

5. The Designee (Multi-Center Coordinating Center specialist) will inform the participating site of the successful registration via Fax or email, to include: Participant

case number

6. A separate Multi-Center Coordinating Center specialist (19-792 Unblinded Contact, or back-up) will inform the participating site's pharmacy contact of the successful randomization via Fax or email, to include Applicable treatment arm assignment, and requests a confirmation

7. Site's pharmacy contact confirms receipt of patient's assignment via email to 19-792 Unblinded Contact (or back-up)

8. The Designee (Multi-Center Coordinating Center specialist) emails Site Team to confirm pharmacy contact has received patient's randomization assignment

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered and randomized.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.7.2 Initiation of Therapy

Participants must be centrally registered with the Multi-Center Coordinating Center and the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.7.4 Unblinding

The day after a participant's scheduled surgery, the Multi-Center Coordinating Center will email the participating site team to confirm participant's surgery. Once surgery has been confirmed, the Multi-Center Coordinating Center specialist will obtain the participant's randomization assignment from the 19-792 Unblinded Contact (or back-up) and will email the unblinded treatment assignment to the Participating Site Team. If patient is in Group C, the Participating Site Team will need to provide patient's SOC treatment plan as soon as possible. Once participant's adjuvant therapy is known (Group A or B)/confirmed (Group C), the Multi-Center Coordinating Center specialist will Register the participant centrally to his/her Step 2 Adjuvant Therapy and will email the Participating Site Team to confirm Step 2 Registration. **NOTE: Adjuvant treatment may not begin without**

confirmation from the Coordinating Center that the participant has been registered to Step 2.

3.8 DF/HCC Protocol Case Number

At the time of registration, DFCI Multi-Center Coordinating Center requires the following identifiers for all participants: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the participant.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and Overall PI and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating

Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Protocol violations occurring at a Participating Institution will be submitted to that site's own IRB per the IRB's reporting policy. Whether or not a violation needs to be reported to the local IRB, notification to the Coordinating Center of any violation should occur in a timely manner. If a report is made to the Participating Institution's IRB, the report and determination should also be forwarded to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor, Overall PI, and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy, and to VBL.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating

investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

DF/HCC RIO develops case report forms (eCRFs) for use with the protocol. These forms are designed to collect data for the study. DF/HCC RIO provides a web based training for all eCRF users.

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of VB-111 for this trial is described below:

VB-111 *(Investigational: for all patients)*: Participating Institutions will order their own supply of VB-111 directly from the VB-111 drug depot using the Drug Supply Request Form (Appendix D to this protocol). First box to be order after first screening. Additional supply should be requested when the local stock is two doses (4 vials). Please allow for 1 week for drug to arrive after the order is submitted. The Participating Institution will ensure that the pharmacy will be able to receive and store the agent according to state and federal guidelines. The local IRB should be kept informed of who will supply the agent (i.e., VBL) so that any regulatory responsibilities can be met in a timely fashion.

5.0 MONITORING: QUALITY CONTROL

Monitoring and oversight of a clinical trial are federally mandated for all IND held trials. This quality control process for a clinical trial requires verification of protocol compliance and data accuracy and the protection of the rights and welfare of participants. The Coordinating Center, with the aid of the ODQ, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institutions may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Remote monitoring of participant eligibility, the initial informed consent process, and screening evaluation completion will occur via a two-stage process.

- Prior to registering each participant, a Coordinating Center Specialist will review the source documentation provided in the enrollment packet to confirm, (a) that based on all objective measurements (lab tests; pathology report) that the prospective participant is eligible, (b) that the objective measurements were performed per protocol within the appropriate protocol-defined windows, (c) that the prospective participant does not have concomitant medication that precludes eligibility, and, if documentation is provided, (d) that the consenting process was adequate/adequately documented, (e) that the participant met criteria for eligibility. Furthermore, using

the Eligibility Screening Worksheet, the Specialist will verify that the investigator has indicated that s/he has reviewed and confirmed as "eligible" the prospective participant

- A Coordinating Center Specialist will review the second set of participant-specific source documents provided by study teams to confirm that (a) all screening and baseline assessments were completed per protocol, including AE assessment, and documented appropriately, (b) that all eligibility criteria were met and appropriately documented, and, if not previously reviewed, (c) that the consenting process was adequate/adequately documented. The timeline for this review will be based on the experience with the study team, and the study team's experience with the protocol.

Interim monitoring visits will occur on the following schedule:

- Once a site has registered a participant, up until all participants (and planned participants) have discontinued taking study agent (may be in follow-up), interim monitoring visits will occur at least twice per year (either on-site or virtual). The first interim monitoring visit will occur approximately two months after the registration of the site's first participant.
- Once a site is closed to accrual and all participants have discontinued study agent, interim monitoring visits will occur virtually, and on-site as needed.

On-Site Monitoring: On-site monitoring will occur on a regular basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact participant safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled.

Virtual Monitoring: The Coordinating Center will request source documentation from participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

Regular all-sites teleconferences will be hosted on a monthly basis by the Coordinating Center (unless otherwise specified by the Overall PI). During the teleconferences, sites should convey the following information:

- Updates on participants: holds, dose reductions, significant events, how participant is doing, date of progression and date of death when available and if not already communicated to the Coordinating Center
- Protocol status: which version is being used, and the status of any amendments
- Any Reportable Adverse Events or Deviations/violations that have yet to be communicated to the Coordinating Center (informing the sponsor should not wait

for the call, and the call does not supplant communicating the events via the regular email methods of communication).
- Review of prospective participants

If sites are not able to have a representative participant, they should email this information to the Coordinating Center.

During the teleconferences, the Coordinating Center may discuss any or all of the following information:
- Accrual/enrollment updates
- Pending amendments
- Safety reports circulated or to be circulated
- ODQ-generated numbers and percentage of missing of missing forms, number of open queries with date of oldest open query, and, for participants on treatment, the date of their last study agent form
- Review of new deviations, violations
- Review of recently received expedited adverse events

The sponsor will have monthly calls with VBL to convey study updates.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

Accrual expectations for Participating Institutions: As this is a Phase II trial, Study Sponsor is requesting that each participating site accrue at least 3 patients annually.

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX C: REPORTABLE AE COVERSHEET

DF/HCC Protocol No. 19-792 VBL Protocol No. TBD

Date:_____ Number of pages including cover sheet:_____

To *(check off recipient of this submission)*:

☐ Patrick Wen, MD (Overall PI) @ Dana Farber Cancer Institute: NeuroOnc_SAE@dfci.harvard.edu
Please e-mail coversheet and MedWatch with the words "19-792 VB-111 SAE" in the subject line

☐ VBL Therapeutics, Attention: Worldwide Product Safety; vblsafety@vblrx.com

From:	Phone No:
Study Site:	Fax No.:
Participant # and Initials:	Participant Cohort (If Known)
Type of Report: ☐ Initial ☐ Follow-up	Was Patient Hospitalized? ☐ Yes ☐ No
Date Event 1st Met Reporting Criteria *(as defined in protocol)*:	Date Investigator Team Made Aware of Event:

(Please use another sheet if more than 2 events being reported at this time)

Event #1 Description *(CTCAE v. 5 term)*:	Event #2 *(if applicable)* Description *(CTCAE v. 5 term)*:
Meets Protocol Definition of Serious AE? ☐ Serious ☐ Non-serious	Meets Protocol Definition of Serious AE? ☐ Serious ☐ Non-serious
Toxicity Grade: ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5	Toxicity Grade: ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5
Historical/Known Correlation to VB-111: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*	Historical/Known Correlation to VB-111: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*
Attribution to VB-111 or Placebo: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	Attribution to VB-111 or Placebo: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Is participant in Group C and post-surgery (receiving SOC): ☐ Yes ☐ No If yes, please complete next 3 questions. Otherwise, consider them Not Applicable. • What Is Patient's SOC Regimen?_____	
Historical/Known Correlation to SOC: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*	Historical/Known Correlation to SOC: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*
Attribution to SOC: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	Attribution to SOC: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Reporting Investigator:	

Signature of Investigator:_____Date:_____

APPENDIX D: DRUG SUPPLY REQUEST FORM

PCI Rockford Manual Shipment Request

Please complete below form and email to CTOrders-US@pciservices.com

Customer	VBL	**Date of Request**	
Protocol	DF/HCC 19-792	**Courier**	Fed Ex
CP #	42872226	**Account Number**	PCI Account
*** LMD Effective: Yes or No**	Yes	**Standard or Rush**	Standard
Order Reference:		**Requested By:**	

Section 1: Consignee Address Details

Site Name & Address – Receipt To (If Applicable)	
Site No	
Investigator name	
Contact Person/Attn	
Email Address	
Contact Phone No	

PCI Item #	Description	Bulk Lot # / Kit Range	PCI Lot or Kit Seq Range	Quantity
629793	Vial Kit for DF/HCC 19-792	VB111VTxx	N/A	1 box including 6 vials

Section 3: Special Conditions – Check all that apply

Ambient	☐		Dry Ice -80°C	☒		Jit Labelling Required	☐
Controlled Ambient	☐		LN2	☐		DEA Schedule I	☐
Refrigerated 2-8°C	☐		Temptale Required	☐		DEA Schedule II	☐
Frozen -20°C	☐		Instructions Required	☐		DEA Scheduled III-V	☐
Notes:							