CLINICAL STUDY PROTOCOL

AMENDMENT 7

A Randomized, Multicenter, Adaptive Phase 3 Study of DSP-7888 Dosing Emulsion in Combination with Bevacizumab versus Bevacizumab Alone in Patients with Recurrent or Progressive Glioblastoma Following Initial Therapy

Protocol Number:	BBI-DSP7888-201G
EudraCT Number:	Not Applicable
INC Research (A Syneos Health Group Company) Study Number:	1009238
Investigational Product:	Nelatimotide and Adegramotide (Ombipepimut-S) (hereafter referred to as DSP-7888) Dosing Emulsion
Phase:	Phase 3
Sponsor:	Sumitomo Dainippon Pharma Oncology Inc. (SDP Oncology) 640 Memorial Drive Cambridge, MA 02139 USA
Contract Research Organization:	INC Research (A Syneos Health Group Company) 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 United States

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1 PROTOCOL APPROVAL SIGNATURES

3 SYNOPSIS

Protocol Number:

BBI-DSP7888-201G

Protocol Title:

A Randomized, Multicenter, Adaptive Phase 3 Study of DSP-7888 Dosing Emulsion in Combination with Bevacizumab versus Bevacizumab Alone in Patients with Recurrent or Progressive Glioblastoma Following Initial Therapy

Investigational Product:

DSP-7888 Dosing Emulsion

Study Centers:

Approximately 70 investigational sites in the US, Canada, Japan, Taiwan, and South Korea

Phase:

Phase 3

Objectives:

Primary objective: The primary objective is to compare the overall survival (OS) between treatment with DSP-7888 Dosing Emulsion plus bevacizumab (Bev) versus Bev alone in patients with recurrent or progressive glioblastoma (GBM) following initial therapy.

Key secondary objective: To compare the 12-month survival rate between treatment with DSP-7888 Dosing Emulsion plus Bev versus Bev alone.

Other secondary objectives:

- To compare the progression-free survival (PFS) of DSP-7888 Dosing Emulsion plus Bev to Bev alone
- To compare the 6-month PFS of DSP-7888 Dosing Emulsion plus Bev to Bev alone
- To compare the response rate of DSP-7888 Dosing Emulsion plus Bev to Bev alone
- To compare the duration of response of DSP-7888 Dosing Emulsion plus Bev to Bev alone

- To describe the adverse event (AE) profile of DSP-7888 Dosing Emulsion plus Bev

Exploratory objectives:

- To describe the relationship between pharmacodynamic parameters such as Wilms' Tumor 1 (WT1) peptide-specific cytotoxic T lymphocyte (CTL) activity and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion plus Bev

- To describe the relationship between expression of WT1 by immunohistochemistry (IHC) and chromogenic in situ hybridization (CISH) in tumor tissue and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion plus Bev

- To collect diffusion-weighted imaging (DWI) for future analysis of imaging findings and correlation with disease progression

- To characterize the Neurological Assessment in Neuro-Oncology (NANO) scale score profile post DSP-7888 Dosing Emulsion plus Bev or Bev alone

Study Design:

This study is divided into 2 parts. Part 1 is a safety lead-in phase. Part 2 is a randomized, active-controlled, multicenter, open-label, parallel-group, adaptive Phase 3 study of DSP-7888 Dosing Emulsion plus Bev versus Bev alone in patients with recurrent or progressive GBM following treatment with first line therapy consisting of surgery and radiation with or without chemotherapy. An adaptive Phase 3 design with 2 interim analyses (IAs) and 1 final analysis (FA) is employed in Part 2 of this trial.

Patients may have undergone a second surgery at the time of recurrence or progression but may not have received any other anti-neoplastic therapy. Patients are randomized 1:1 to treatment with DSP-7888 Dosing Emulsion plus Bev or Bev alone.

Potential study subjects first undergo pre-screening to determine appropriate human leukocyte antigen (HLA) type due to the nature of the vaccine DSP-7888. DSP-7888 Dosing Emulsion is active in subjects with HLA-A*02:01, HLA-A*02:06, or HLA-A*24:02.

Following HLA determination, a screening phase of up to 28 days determines eligibility. Following verification of eligibility and enrollment, DSP-7888 Dosing Emulsion is administered intradermally (i.d.) every 7 days (± 1 day) for 5 doses (the Induction Phase); then every 14 days (± 3 days) for Doses 6 to 15 (the Consolidation Phase), and then every 28 days (± 7 days) for Doses 16 and above (the Maintenance Phase). Bev is administered every 14 ± 3 days at the labeled dose of 10 mg/kg intravenously (i.v.).

Part 1:

In Part 1, 3 patients will be treated with the combination of DSP-7888 Dosing Emulsion plus Bev in a single-arm manner. DSP7888 Dosing Emulsion will be administered at a dose of 10.5 mg i.d. per the schedule described above and Bev at the dose and schedule described above. If 0 of these first 3 patients experiences dose-limiting toxicity (DLT), then the study will proceed to Part 2, which will randomize patients to the combination of DSP-7888 Dosing Emulsion plus Bev or to Bev alone.

If 1 of the first 3 patients experiences a DLT, then 3 more patients will be enrolled at the same treatment regimen. If no additional DLTs are observed at the same dose (with 1/6 DLTs), then the study will proceed to Part 2. However, if 2 or more of the first 6 patients experience a DLT, then the dose of DSP-7888 Dosing Emulsion will be decreased to 3.5 mg i.d., and an additional 3 patients will be treated with the combination of DSP-7888 Dosing Emulsion plus Bev.

If 0 of these 3 patients experiences DLT at this reduced dose of DSP-7888 Dosing Emulsion, then the study will proceed to Part 2. If 1 of the 3 patients experiences a DLT at the reduced dose of DSP-7888 Dosing Emulsion, then 3 more patients will be enrolled at the same treatment regimen. If no additional DLTs are observed at the same dose (with 1/6 DLTs), then the study will proceed to Part 2. However, if 2 patients or more experience a DLT at this reduced dose of DSP-7888 Dosing Emulsion plus Bev, then enrollment will be placed on hold until the Sponsor decides how best to proceed.

In summary, if 0 of the first 3 patients or 1 of the first 6 patients experience a DLT, then the study will proceed to Part 2. The maximum tolerated dose (MTD) is decided only when 6 patients are treated at a dose level with ≤ 1/6 DLT. If at least 2/3 or 2/6 DLTs are observed, then the MTD has been exceeded. Dosing should stop, and the dose should be de-escalated to DSP-7888 3.5 mg. Then the process should be repeated at the reduced dose level of DSP-7888 3.5 mg.

The patients who complete Part 1 of the study will not be randomized into Part 2. Instead, they will continue to receive DSP-7888 Dosing Emulsion plus Bev and undergo the same assessments that are listed for Part 2 of the study.

Dose-limiting toxicity will be evaluated and applied during the Induction Phase of Part 1 (Day 1 through Day 29) and defined as the following AEs that are at least possibly related to the investigational agents per the Investigator and institutional guidelines:

- The occurrence of any Grade 3 or higher hematologic AE lasting more than 7 days;

- Any Grade 3 or higher non-hematological AE that persists for more than 72 hours with the exceptions of transient nausea, vomiting, and diarrhea that are responding to supportive care;
- Any Grade 3 or higher allergic and/or hypersensitivity reactions; and,
- Any Grade 2 or higher autoimmune disease.

Patients who discontinue Part 1 of the study for reasons other than DLT during the Induction Phase will be replaced.

Part 2:

Based on the results of the DLT evaluation in Part 1, a 10.5-mg dose of DSP-7888 Dosing Emulsion was determined as the dose for Part 2.

In Part 2, patients are stratified prior to randomization based on the extent of surgical resection in primary therapy (gross total resection [GTR] versus not GTR) and Karnofsky Performance Status (KPS) scores (60 through 70 versus 80 through 100).

Rescreening for patients in Part 2 is permitted for patients with laboratory values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, creatinine) that are out of range to meet eligibility and for patients requiring dexamethasone doses in excess of 4 mg/day (or equivalent) once the dose can be tapered to 4 mg/day (or equivalent) or less with stability in the judgement of the investigator.

Patients will continue to receive DSP-7888 Dosing Emulsion plus Bev or Bev alone independent of radiological assessment / progression:

1. Provided that the Investigator considers it to be safe for the patient
2. Provided that the Investigator determines that there is potential benefit for the patient
3. When the patient is willing to continue

Safety is assessed by the recording of AEs at each contact with the patient, by findings of physical and neurological examinations, and by the results of laboratory determinations; the severity of AEs or abnormal laboratory results is based on the Common Terminology Criteria for Adverse Events (CTCAE) V4.03.

The criteria for response and progression is based on the Modified Response Assessment in Neuro-Oncology (mRANO) criteria, and patients also undergo neurological assessments based on the NANO criteria.

Patients randomized to the Bev arm of the study undergo evaluations on a similar schedule as patients randomized to treatment with the combination of DSP-7888 Dosing Emulsion plus Bev.

Patients undergo magnetic resonance imaging (MRI) and DWI to assess their disease progression. Patients who are, in the opinion of the Investigator, clinically stable and in whom pseudo-progression is suspected will continue to be treated per protocol according to the treatment arm assigned and will have a second (confirmatory) scan performed 4-8 weeks later.

Patients who discontinue study treatment for any reason will continue to be followed up for efficacy (mRANO, NANO, KPS, etc.) until new treatment is commenced.

All patients are followed up for OS, regardless of potential subsequent therapy.

Patients' immunological responses to DSP-7888 Dosing Emulsion are measured by a variety of assays including:

- Measurement of WT1 peptide-specific CTL induction activity at various times using peripheral blood mononuclear cells of patients
- Retrospective analysis of additional biomarkers from peripheral blood and archival tumor samples

Formalin-fixed, paraffin-embedded (FFPE) archival tumor samples will be tested for expression of WT1 by IHC and CISH and compared to a variety of clinical outcomes in exploratory analyses. Additional exploratory analyses will evaluate the role of DWI in predicting and diagnosing true progression of neoplastic disease in patients with GBM. Exploratory analyses will be performed to investigate the relationship between DSP-7888 Dosing Emulsion activities and other HLA Class 1 haplotypes (A and B locus) as well as HLA Class 2.

Companion diagnostics of HLA typing will be developed as part of this study.

Number of Patients:

Between 3 and 12 patients were planned to be enrolled in Part 1 of the study (Section 8.1.1). As of Protocol Amendment 7, 4 patients had been enrolled into Part 1.

For Part 2, the adaptive Phase 3 study design, if the study continues to the final analysis with appropriately 260 death events (Section 8.2.1), approximately 338 patients with GBM will be enrolled from approximately 70 investigational sites in the United States (US), Canada, Japan, Taiwan, and South Korea. Part 2 of the study may be concluded earlier with early efficacy at IA2 or may be concluded in the final analysis with re-estimated number of

death events. Note that Part 2 of the study is an event-driven adaptive trial and statistical power of Part 2 is determined by the target number of death events instead of the number of patients. The actual number of randomized patients in Part 2 may be adjusted to observe the targeted number of events, depending on the outcome of the interim analyses and operational feasibility.

Treatment:

Part 1: This part of the study is a safety run-in cohort to determine the recommended dose (RD) for Part 2. The initial dose of DSP-7888 Dosing Emulsion is 10.5 mg. Bev will be administered at a dose of 10 mg/kg by i.v. infusion.

Note: The dose of DSP-7888 Dosing Emulsion may be reduced for individual patients to 3.5 mg or 1.75 mg if any dose reduction criterion is met.

Part 2: Based on the results of the DLT evaluation in Part 1, a 10.5 mg dose of DSP-7888 Dosing Emulsion was determined as the dose for Part 2. Bev is administered at a dose of 10 mg/kg by i.v. infusion.

Note: The dose may be reduced for individual patients to 3.5 mg or 1.75 mg of DSP-7888 Dosing Emulsion if any dose reduction criterion is met.

Study Duration:

The study duration for individual patients commences at date of pre-screening consent and completes at the date of End of Study visit. The study will continue until the target number of events is observed. The study may be terminated early for efficacy or futility at the planned interim analyses. Individual patient OS status will be followed until the end of the study.

Study Population:

The study will enroll patients with GBM whose tumors have recurred or progressed following initial treatment with surgery, radiation, and/or chemotherapy.

Inclusion Criteria

Patients must fulfill all the following requirements:

1. Patients or their legal representatives must be able to provide written informed consent.

2. Histologically confirmed diagnosis of supratentorial GBM (Grade 4 astrocytoma).

3. Radiographic evidence of first recurrence or progression of GBM following primary therapy consisting of surgery (biopsy or resection) and radiation with or without chemotherapy; patients may have undergone a second debulking surgery following initial recurrence or progression. Patients whose tumors are O^6-methyl-guanyl-methyl-transferase (MGMT) methylated-promoter negative need not have received chemotherapy in the past to be eligible.

4. Human leukocyte antigen type HLA-A*02:01, HLA-A*02:06, or HLA-A*24:02.

5. Age ≥ 18.

6. KPS score of ≥ 60.

7. Serum creatinine value < 2X the upper limit of normal (ULN) for the reference laboratory.

8. ALT and AST < 3X the ULN and total bilirubin < 2X the ULN for the reference laboratory.

9. Men and women of childbearing potential must agree to use a reliable method of contraception (oral contraceptives, implantable hormonal contraceptives, or double barrier method) or agree to completely refrain from heterosexual intercourse for the duration of the study and for 180 days following the last dose of DSP-7888 Dosing Emulsion.

10. Patients must have recovered from the effect of all prior therapy to Grade 2 or less.

11. Patients must be at least 28 days from any major surgery, and any surgery incisions or wounds must be completely healed.

12. Patients must be at least 12 weeks from the completion of prior radiation therapy (RT) in order to discriminate pseudo-progression of disease from progression.

13. Patients must be at least 4 weeks from the completion of prior systemic or intracranial chemotherapy.

14. Patients must stop Novo-TTF treatment one day prior to study therapy (no washout period is needed). However, any wounds from TTF must be adequately healed per Inclusion Criterion #11.

15. For patients who are not receiving therapeutic anticoagulation treatment, an international normalized ratio (INR) and a partial thromboplastin time (PTT) ≤ 1.5X the ULN; patients who are receiving anticoagulation treatment should be on a stable dose.

16. Patient's left ventricular ejection fraction (LVEF) > 40%.

17. Patient has a resting pulse oximetry of 90% or higher.

Exclusion Criteria

Patients will be excluded from the study if one or more of the following are applicable:

1. Prior therapy with Bev.

2. Patients with secondary GBM.

3. Any anti-neoplastic therapy, including RT or laser interstitial thermal therapy, for first relapse or recurrence.

4. Evidence of leptomeningeal spread (gliomatous meningitis) of tumor or any history, presence, or suspicion of metastatic disease extracranially.

5. Evidence of impending herniation on imaging.

6. Has known multifocal disease. Multifocal disease is defined as discrete sites of disease without contiguous T2/FLAIR abnormality that require distinct radiotherapy ports. Satellite lesions that are associated with a contiguous area of T2/FLAIR abnormality as the main lesion(s) and that are encompassed within the same radiotherapy port as the main lesion(s) are permitted.

7. Patients with infections that have required treatment with systemic antibiotics within 7 days prior to the first dose of protocol therapy.

8. The need for systemic glucocorticoids in doses in excess of 4 mg/day of dexamethasone or in comparable doses with other glucocorticoids.

9. Treatment with any investigational agents within 5 half-lives of the agent in question or, if the half-life is unknown, within 28 days of enrollment.

10. Pregnant or lactating females.

11. Prior history of malignancy within 3 years of enrollment other than basal or squamous cell carcinoma of the skin, cervical intra-epithelial neoplasia, in situ carcinoma of the breast, or localized prostate cancer treated with surgery or RT with a prostate specific antigen of < 0.01 ng/mL.

12. Patients with active autoimmune diseases within 2 years of enrollment into the study including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus,

systemic sclerosis, Sjogren's syndrome, Wegener's granulomatosis, ulcerative colitis, Crohn's disease, myasthenia gravis, Graves' disease, or uveitis except for psoriasis not requiring systemic therapy, vitiligo or alopecia areata, or hypothyroidism; if an autoimmune condition has been clinically silent for 12 months or greater, the patient may be eligible for enrollment.

13. Patients on immunosuppressive therapies; the use of topical, inhalational, ophthalmologic, or intra-articular glucocorticoids or the use of physiologic replacement doses of glucocorticoids is permitted.

14. Patients with primary immunodeficiency diseases.

15. Patients with significant bleeding in the preceding 6 months prior to study enrollment or with known coagulopathies.

16. History of abdominal fistula, intestinal perforation, or intra-abdominal abscess in the preceding 12 months prior to study enrollment

17. Positive serology for human immunodeficiency virus (HIV) infection, active hepatitis B*, or untreated hepatitis C; patients who have completed a course of anti-viral treatment for hepatitis C are eligible.

    *In cases of negative results for HepB surface antigen with positive HepB core antibody, HBV deoxyribonucleic acid (DNA) testing is required.

18. Patient has a medical history of frequent ventricular ectopy, eg, non-sustained ventricular tachycardia (VT).

19. Significant cardiovascular disease, including New York Hospital Association Class III or IV congestive heart failure, myocardial infarction within 6 months of study enrollment, unstable angina, poorly controlled cardiac arrhythmias, or stroke in the preceding 6 months prior to study enrollment.

20. Any other uncontrolled inter-current medical condition, including systemic fungal, bacterial, or viral infection; uncontrolled hypertension; diabetes mellitus; or chronic obstructive pulmonary disease requiring 2 or more hospitalizations in the preceding 12 months prior to study enrollment.

21. Any psychiatric condition, substance abuse disorder, or social situation that would interfere with a patient's cooperation with the requirements of the study.

22. Known sensitivity to Bev or any of the components of DSP-7888 Dosing Emulsion.

23. Patient has a QTcF (QT corrected based on Fridericia's equation) interval > 480 msec (CTCAE = Grade 2) or other factors that increase the risk of QT prolongation or

arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) at screening. (Patients with bundle branch block and a prolonged QTc interval should be reviewed by the Medical Monitor for potential inclusion.)

24. Patient has dyspnea at rest (CTCAE ≥ Grade 3) or has required supplemental oxygen within 2 weeks of study enrollment.

Primary Endpoint:

The primary endpoint is OS and is defined as the interval between randomization and death from any cause. Patients who are lost to follow-up will be censored on the last day they were known to be alive.

Key Secondary Endpoint:

The key secondary endpoint is the12-month survival rate and is defined as the proportion of patients alive 12 months after randomization.

Other Secondary Endpoints:

- PFS is defined as the interval between randomization and progression, determined by the central radiology review or death from any cause.
- 6-month PFS rate is defined as the proportion of patients alive at 6 months after randomization and without progressive neoplastic disease.
- The response rate is defined as the proportion of patients exhibiting a response (complete response [CR] plus partial response [PR]) based on the mRANO criteria as determined by the central radiology review.
- The duration of response is defined as the interval between first documented oncological response and progression of disease or death from any cause, with response based on the mRANO criteria as determined by the central radiology review.

Efficacy:

Efficacy will be evaluated by comparing the OS between treatment with DSP-7888 Dosing Emulsion plus Bev versus Bev alone in patients with recurrent or progressive GBM following initial therapy.

Pharmacodynamics:

The relationship between pharmacodynamic parameters such as WT1 peptide-specific CTL activity and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion will be described if appropriate.

The relationship between the expression of WT1 by IHC and CISH in tumor tissue and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion will be described if appropriate.

Safety:

The Sponsor will promptly review all serious life-threatening and fatal events (other than death due to disease progression) reported in the study and perform a causality assessment.

Based on the causality assessment of life-threatening and fatal events that occur from the start of treatment with DSP-7888 Dosing Emulsion and up to 30 days from the last dose of DSP-7888 Dosing Emulsion (other than death due to disease progression), the Sponsor will determine whether the study will be suspended for safety review.

The Sponsor will determine whether the study will be modified, continue enrollment or be terminated based on the following scenarios:

- Any cases of death (other than death related to progressive disease) that occur from the start of treatment with DSP-7888 Dosing Emulsion and up to 30 days from the last DSP-7888 Dosing Emulsion administration and deemed by the Sponsor to be related to any of the study's drugs.
- If the percentage of patients presenting with drug-related (assessed by Sponsor) Grade 4 or higher AE within a particular medical concept (eg, hypersensitivity) in this study is higher than that reported in patients treated with DSP-7888 Dosing Emulsion within the clinical program and as reported in the literature for GBM patients.

The causality assessment and safety reviews will occur in the context of the Sponsor's safety governance processes including the study team and senior leadership. As part of the safety review, in addition to ongoing routine review of the safety data by the Independent Data Monitoring Committee (IDMC), the Sponsor may choose to consult with the IDMC on an ad hoc basis.

Based on the safety review, the Sponsor will determine whether the study may continue (with or without a protocol amendment) or if it must be terminated.

Statistical Analysis:

The OS will be estimated using Kaplan-Meier (KM) estimates and will be tested using a stratified log-rank test considering the randomization strata of extent of surgical resection in primary therapy (GTR versus not GTR) and KPS class (60 through 70 versus 80 through 100) in the intent-to-treat (ITT) population. The 12-month OS rate will be estimated based on the 12-month KM estimate. A comparison between treatments will be performed using a Z-test-statistic considering the respective Greenwood variances. PFS and duration of response will be analyzed similarly to OS. The 6-month PFS rate will be analyzed similarly to the 12-month survival rate. The proportion of patients who achieve CR or PR will be analyzed using a Cochran-Mantel-Haenszel method considering the 2 randomization factors. Stratified Cox-Proportional-Hazards regression, stratified by the 2 randomization factors, will be used to assess the hazard ratio (HR) for the comparison of the treatments.

Sample Size:

Considering that the number of death events are 108 (observed at interim analysis 1 [IA1]), approximately 185 (interim analysis 2 [IA2]), and approximately 260 (FA), then the study will have approximately 90% power to detect a 34% reduction in the HR of DSP-7888 Dosing Emulsion plus Bev versus Bev alone (ie, HR = 0.663, which corresponds to a 1-year survival proportion of 45% in the DSP-7888 Dosing Emulsion plus Bev arm compared to 30% in the Bev alone arm). The number of death events at the FA could go up to 370 if event re-estimation is performed based on the conditional power calculated at IA2. Assuming an enrollment rate of 11 patients per month and patients are followed until the end of the study, with a 5% dropout rate per year, the study will require enrolling of approximately 338-480 patients.

Note that Part 2 is an event-driven adaptive trial and statistical power of Part 2 is determined by the target number of death events instead of the number of patients. The actual number of randomized patients in Part 2 may vary to observe the targeted number of events, depending on the outcome of the interim analyses, the duration of the study and operational feasibility. It is envisioned that approximately 215 patients will be enrolled at the second IA with 185 events, approximately 338 patients will be enrolled at the FA with 260 events when there is no event number re-estimation. If the number of events at the FA reaches the cap of 370 with event number re-estimation, approximately 480 patients will be enrolled in the study assuming that the ratio of the number of events to the number of patients at the FA is approximately 0.77 (assume similar death event rate of 260/338 when the target event number is 260).

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5 LIST OF ABBREVIATIONS & DEFINITIONS

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKT	serine/threonine kinase also known as protein kinase B
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Bev	Bevacizumab
BBI	Boston Biomedical, Inc.
CBC	complete blood (cell) count
CFR	Code of Federal Regulations
cGCP	current Good Clinical Practice
CI	confidence interval
CISH	chromogenic in situ hybridization
CP	conditional power
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSP	Sumitomo Dainippon Pharma
DSP-7888	adegramotide/nelatimotide (INN, International Non-Proprietary Names) or ombipepimut-S (USAN, United States Adopted Name)
DSP-7888 Dosing Emulsion	adegramotide/nelatimotide suspension with montanide
DSP-7888-H	DSP-7888 (adegramotide [INN]) helper peptide
DSP-7888-K	DSP-7888 (nelatimotide [INN]) cytotoxic T lymphocyte-inducing (killer) peptide

DSP-7888-M	water-in-oil emulsion of DSP-7888 with the immunogenicity enhancing adjuvant MONTANIDE ISA 51 VG
DWI	diffusion-weighted imaging
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EGFRvIII	epidermal growth factor receptor vIII tumor-specific oncogene
EOT	end of treatment
FA	final analysis
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GBM	glioblastoma
GTR	gross total resection
Hep	hepatitis
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
IA	interim analysis
IA1	interim analysis 1
IA2	interim analysis 2
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.d.	intradermally
IDH	isocitrate dehydrogenase
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGF1R	type 1 insulin-like growth factor receptor
IHC	immunohistochemistry

INR	international normalized ratio
IRB	Institutional Review Board
IRES	internal ribosome entry site
ISR	injection site reaction
ITT	intent-to-treat
i.v.	intravenously
KLH	keyhole limpet hemocyanin
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MAP	mitogen activated protein
MDS	myelodysplastic syndromes
MGMT	O^6-methyl-guanyl-methyl-transferase
MHC	major histocompatibility complex
mRANO	Modified Response Assessment in Neuro-Oncology
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
n	number of patients with an observation
NA	not available, not applicable, or not able to assess
NANO	Neurological Assessment in Neuro-Oncology
O_2	oxygen
OK-432	picibanil antitumor agent
ORR	overall response rate
OS	overall survival
P53	tumor suppressor protein
PD	progressive disease
PDGF-A	platelet-derived growth factor A

PE38QQR	*Pseudomonas aeruginosa* exotoxin A
PFS	progression-free survival
PFS6	6-month progression-free survival
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PP	per protocol
PR	partial response
PTT	partial thromboplastin time
PVS-RIPO	poliovirus-rhinovirus IRES poliovirus open reading frame
QTcF	Fridericia's correction formula (msec)
RANO	Response Assessment in Neuro-Oncology
RD	recommended dose
RNA	ribonucleic acid
RT	radiation therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDP Oncology	Sumitomo Dainippon Pharma Oncology, Inc
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
VEGFR	vascular endothelial growth factor receptor
VT	ventricular tachycardia
WBC	white blood (cell) count
WHO	World Health Organization
Wnt	Int/Wingless gene family combining nomenclature of integration 1 (int 1) and Wingless (Wg) genes
WT1	Wilms' Tumor 1

6 INTRODUCTION

6.1 Disease

It is estimated that in 2017, there will be 23,800 new cases of brain and nervous system tumors in the US alone; and there were 255,000 cases worldwide in 2012.[1,2] The age adjusted incidence rate of brain tumor in the US is 6.4/100,000, and this rate has been relatively stable over several decades.[3] Gliomas, sub-types of brain tumors, are malignant neoplasms of glial tissue and are derived from astrocytes. The World Health Organization (WHO) further divides gliomas into several sub-types; GBM is classified as a Grade 4 astrocytic tumor due to its highly malignant potential.[4] Gliomas comprise 81% of all brain tumors, and GBMs comprise 45% of all gliomas.[5] The incidence of GBM increases with age, starting around age 55, reaching a peak in the 75- to 84-year-old age group, after which the incidence declines. [6]

Even though GBM rarely spreads distantly, progressive expansion of the tumor within the fixed confines of the bony skull results in significant morbidity and mortality. The survival of GBM is extremely poor; 5-year survival rates are consistently under 5%, whether in the US,[6] the European Union[7] or Asia.[8] Glioblastoma, therefore, remains a disease with a significant unmet medical need.

6.1.1 Current Therapy of Glioblastoma

Following the initial diagnosis of GBM, a majority of patients undergo maximal resection, followed by RT and adjuvant temozolomide. This recommendation is based on a randomized study comparing surgery, radiation, and temozolomide to surgery and radiation alone, where the 3 modality treatment regimen was shown to be statistically significantly better than surgery and radiation alone.[9] Two-year survival for the 3 modality regimen was 27.2% versus 10.9% for the 2 modality regimen; and these differences persisted over 5 years of follow-up (HR = 0.6, $p < 0.0001$). No new drugs or therapies have been shown to have clinical benefit in the first line treatment of GBM since the publication of these data.

Bevacizumab (AVASTIN®) is approved for the second-line treatment of GBM. This approval was based on 2 open-label studies conducted in patients with recurrent GBM. The first study was a single-arm study of Bev in 48 patients with recurrent GBM (any recurrence). In this study, the overall response rate (ORR) was 35%, the 6-month PFS was 29%, and the median OS was 31 weeks.[10] The second study randomized patients in first or second recurrence to Bev alone (n = 85) or the combination of Bev and irinotecan (n = 82). In the monotherapy arm, the ORR was 28%, the 6-month PFS was 43%, and the median OS was 37 weeks, consistent with the results of the first study.[11] Several other studies involving the combination of Bev and other agents have not shown improvements on these results; and since the approval of Bev, there have been no other systemic therapies approved for the treatment of recurrent GBM.

6.1.2 Recent Studies in Recurrent Glioblastoma

Despite continued efforts at discovering novel agents for the treatment of recurrent GBM, there is an obvious need for a treatment that can improve on the current treatment methods. Several recent studies conducted in patients with recurrent or progressive GBM illustrate the difficulty in developing new agents in this condition.

The PRECISE Study was a global clinical Phase 3 study that randomized 296 patients with first recurrence of GBM to cintredekin besudotox (IL13-PE38QQR), administered via convection enhanced delivery directly into the brain parenchyma, or carmustine implant (GLIADEL WAFER®). Cintredekin besudotox is a recombinant cytotoxin consisting of human interleukin-13 fused to Pseudomonas exotoxin A. All patients underwent gross resection of tumor prior to receiving assigned treatment. The primary endpoint of the study was OS. After the protocol specified cut-off of 215 events, there was no difference in OS between the 2 arms (9.1 months for cintredekin besudotox versus 8.8 months for Gliadel, p = 0.48).[12]

A second Phase 3 multicenter study compared treatment with enzastaurin, a protein kinase Cβ and phosphoinositide 3-kinase (PI3K)/serine-threonine kinase (AKT) inhibitor, to treatment with lomustine in patients with recurrent GBM. The primary endpoint was PFS. A total of 266 patients were randomized 2:1 between enzastaurin and lomustine. An IA for futility was performed after 115 patients had progression or had died. There was no difference in PFS between the 2 treatment arms (1.5 months for enzastaurin, 1.6 months for lomustine). There was also no difference in 6-month PFS (11.1% for enzastaurin, 19% for lomustine), median OS (6.6 months versus 7.1 months), or ORR (2.9% versus 4.3%).[13]

A third Phase 3 multicenter study randomized 325 patients with recurrent GBM (2:2:1) manner to treatment with cediranib, a pan-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor, the combination of cediranib and lomustine and lomustine alone. The primary endpoint of the study was PFS. There were no differences in PFS between treatment with cediranib alone compared to lomustine (92 days for cediranib versus 82 days for lomustine, p = 0.90) or with cediranib in combination with lomustine compared to lomustine (125 days for the combination versus 82 days for lomustine alone, p = 0.16.). There were also no differences in median OS (8.0 months for cediranib, 9.4 months for the combination, and 9.8 months for lomustine) or ORR (15.3% for cediranib, 17.2% for the combination, and 8.9% for lomustine).[14]

These 3 contemporary, randomized Phase 3 studies in recurrent GBM clearly illustrate the challenge in developing new agents for the treatment of GBM.

6.1.3 Wilms' Tumor 1 (WT1) Antigen

6.1.3.1 Molecular Biology and Role in Oncogenesis

The WT1 gene encodes a zinc-finger transcription factor that binds to both DNA and ribonucleic acid (RNA) and, under circumstances of normal embryogenesis, directs the development of several organs and tissues. The WT1-null condition is lethal to developing embryos, in which there is a complete lack of development of the kidneys, the gonads, the heart, the spleen, and the adrenal glands.[15] In healthy adults, expression of WT1 is limited to certain cells of the glomerulus, and reduced expression is associated with glomerulopathies.[16] Although WT1 was originally thought to function solely as a tumor suppressor based on its activity in Wilms' tumor, expression of WT1 in adult tumors points to its possible role as an oncogene. In this respect, numerous target genes for WT1 have been discovered, including genes encoding growth factors and growth factor receptors (epidermal growth factor receptor [EGFR], type 1 insulin-like growth factor receptor [IGF1R], transforming growth factor beta, platelet-derived growth factor A [PDGF-A]; genes involved in wingless-related integration site (Wnt) pathway signaling; genes involved in differentiation; and genes involved in apoptosis (Bcl2, c-Myc).[11,15] A metaanalysis has shown that expression of WT1 by neoplasms negatively impacts OS (metaHR 1.48, 95% confidence interval [CI] = 1.11, 1.97) as well as disease free, relapse-free, and PFS (meta HR = 2.14, 95% CI = 1.42, 3.21).[11,17] Based on data from previous studies using WT1 vaccines, as well as the immunogenicity, oncogenicity, and specificity of WT1, the National Cancer Institute selected WT1 as the highest priority tumor-associated antigen for vaccine development.[18]

6.1.3.2 WT1 in Glioblastoma

Approximately 80% of GBMs express WT1 as a tumor-associated antigen[19] and WT1 seems to contribute to the malignant nature of the disease. When wild-type and WT1 knockdown U87MG GBM cell lines were injected intracerebrally into new-born mice, all control animals were dead by Day 40, whereas all the animals harboring the knockdown cells were alive. In addition, apoptosis related genes, including mitogen-activated protein (MAP) kinase, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and tumor suppressor protein (p53) were up regulated in the knockdown cells compared to the wild-type cells.[20] In another set of experiments with GBM, compared to wild-type cells, WT1 knockdown cells had differential gene expression, with down regulation of several oncogenic genes, and up regulation of genes involved in tumor suppression.[21] Therefore, WT1 would seem to be a critical oncologic element of GBM.

6.1.3.3 Vaccine- and Immune-Based Clinical Studies in Recurrent Glioblastoma

There have been several studies employing various vaccine strategies (peptide, dendritic, cell lysate) in patients with newly diagnosed GBM, but few in patients with recurrent or

progressive GBM. Several recent studies, however, demonstrate the potential role of vaccine therapy in GBM.

The ReACT study was a randomized, placebo-controlled study of rindopepimut, which consists of an EGFRvIII peptide conjugated to keyhole limpet hemocyanin (KLH), in combination with Bev versus KLH plus Bev, in patients with recurrent or progressive GBM following initial treatment with RT and temozolomide. Patients treated with rindopepimut plus Bev (n = 36) had a 6-month PFS (PFS6, the study's primary endpoint) of 28%, versus 16% in the control arm (n = 37, p = 0.0658). In the rindopepimut arm, 9/30 patients (30%) had a radiographic response (CR plus PR) versus 6/34 (18%) of patients in the control arm. OS was 11.3 months in the rindopepimut arm versus 9.3 months in the control arm (HR = 0.53, p = 0.0137). Rindopepimut also elicited a brisk immunologic response as evidenced by measurement of anti-rindopepimut antibodies.[22]

Poliovirus-rhino virus internal ribosome entry site poliovirus open reading frame (PVS RIPO) is an engineered recombinant live attenuated oncolytic virus containing the oral poliovirus Sabin type 1, where the internal ribosome entry site (IRES) has been replaced with the IRES from human rhinovirus type 2. A Phase 1 study in patients with recurrent adult GBM enrolled 24 patients. The median OS was 12.5 months; the 6-month OS was 83%, and the 12-month OS was 56%. There have also been several long-term survivors (in excess of 22 months), and 2 patients have no evidence of disease. The US Food and Drug Administration (FDA) granted PVS-RIPO breakthrough designation for the treatment of GBM.[23]

A Phase 2 clinical study with a WT1 vaccine was conducted in Japan in 21 patients with recurrent GBM (the peptide in this study was different from the peptides contained in DSP-7888 Dosing Emulsion). The vaccine was administered i.d., and treatment was well tolerated with local erythema as the only vaccine-related AE. Partial response was observed in 2 patients, and stable disease (SD) in 10 patients. The median PFS was 20 weeks, and the PFS-6 was 33%. Two patients showed initial responses of progressive disease (PD); however, tumor stabilization occurred 6 months after the start of treatment in the trial, which could be suggestive of pseudo-progression. In addition, a decrease in tumor size was observed in one patient in the SD group (although not achieving the partial response requirements), which was observed 7 months after the initial WT1 vaccination.[24] Two patients showed complete responses that were indicative of pseudo-progression on Days 645 and 505.[25] Finally, a second study of a WT1 vaccine was conducted in Japan in 10 patients with recurrent malignant glioma. This study employed dendritic cells pre-incubated with 2 WT1 peptides, which were then injected i.d. in the axillary region along with OK-432 (picibanil antitumor agent), a streptococcal adjuvant. Approximately 1 to 2 x 10^7 cells were injected every 2 weeks for 5 to 7 administrations. The study enrolled 10 patients; other than injection site reactions (ISRs), the vaccine was well tolerated. Of the 6 patients with GBM, 2 had prolonged survival times of >46 months and >77 months.[26,27]

6.1.3.4 Rationale for Use of Modified Radiographic Response Assessment (mRANO)

GBM often displays high vascularity.[28] For this reason, contrast enhancement on imaging studies such as CT or MRI can be used to determine radiographic response or progression after treatment. Several sets of radiographic criteria have been developed and used in GBM studies to determine tumor response, including the Macdonald criteria[29] and the Response Assessment in Neuro-Oncology (RANO) criteria.[30] RANO criteria were developed to correct deficiencies in the Macdonald criteria, including taking into account non-enhancing tumor progression and the phenomenon of pseudo-progression. Pseudo-progression has emerged as a particularly important concept in GBM studies wherein an increase in contrast enhancement resulting from increased vascular permeability induced by anti-tumor treatment may be mistaken for tumor progression.

The current study will use mRANO to evaluate tumor response. It is recognized that RANO criteria have limitations, including reader discordance in bidimensional tumor measurements of contrast-enhancing tumors,[31] and in the era of immunotherapy, inflammatory changes in the tumor as a result of immune activation may lead to ambiguous changes in T2 signal intensity that are difficult to interpret.[32] mRANO criteria were developed to overcome these limitations. The mRANO criteria allow for continuation of therapy for patients with apparent progression at first imaging or on a subsequent radiographic assessment following a period of SD, PR, or CR. Specifically, the criteria allow patients with "preliminary progression" (defined as a $\geq$ 25% increase in sum of products of bidimensional measurements or $\geq$ 40% volume increase of enhancing lesions) to continue on treatment for at least 4 weeks, at which time a scan should be done to confirm or refute progression. Because delayed responses to WT1 vaccine therapy have been seen (even after apparent initial progression), using a set of radiographic assessment criteria such as mRANO will allow for better discrimination of patients with pseudo-progression from true progression.

Additionally, this protocol will not mandate discontinuation of treatment even if progression is confirmed by mRANO criteria. Currently, there are no radiological assessment criteria that enable a clear differentiation of true progression from pseudo-progression. In studies involving immune activation, pseudo-progression may limit greatly the ability to determine treatment benefit (or lack thereof). Therefore, it is important to allow patients to continue on study treatment for as long as possible to differentiate pseudo-progression from true progression. Thus, the current study will allow patients to continue receiving study treatment despite confirmed mRANO progression provided that the Investigator considers it to be safe, the Investigator determines that there is potential benefit, and the patient is willing to continue.

6.1.4 DSP-7888 Dosing Emulsion

DSP-7888 is a synthetic peptide that consists of 2 synthetic peptide constructs: DSP-7888-K (major histocompatibility complex [MHC] Class I peptide; nelatimotide [INN]) and DSP-7888-H (MHC Class II peptide; adegramotide [INN]). Both constructs are derived from the WT1 protein. Specifically, DSP-7888-K is a conjugate consisting of the $WT1_{126-134}$ peptide sequence and the modified $WT1_{235-243}$ peptide sequence, whereas DSP-7888-H corresponds to the $WT1_{34-51}$ sequence. DSP-7888 Dosing Emulsion is an emulsion of these peptides formulated in a water/oil emulsion with DSP-7888-M, a solution that contains the well-known adjuvant montanide ISA 51 VG. The emulsion acts as a depot and enhances the immunogenicity of the DSP-7888-K and DSP-7888-H peptides. DSP-7888 Dosing Emulsion is applicable for patients who have at least one of 3 HLA types: HLA-A*02:01, HLA-A*02:06, and HLA-A*24:02, which covers approximately 56% of the US population and 81% of the Japanese population.[33]

DSP-7888 Dosing Emulsion is administered i.d. and is presented on the surface of antigen-presenting cells as an MHC Class I peptide complex that can be recognized by CD8 positive CTLs. As a consequence, vaccination with DSP-7888 Dosing Emulsion may stimulate the host immune system to induce a CTL response against cancer cells overexpressing the WT1 protein, resulting in cell lysis and inhibition of cancer cell proliferation. Addition of the MHC Class II peptide is expected to show efficacy over that observed with a treatment regimen of the MHC Class I peptide alone.

DSP-7888 Dosing Emulsion is under clinical investigation in 3 studies: A Phase 1 study in patients with a variety of advanced malignancies in the US, a Phase 1/2 study in patients with myelodysplastic syndrome (MDS) in Japan, and a Phase 1/2 study in children with malignant glioma in Japan. DSP-7888 Dosing Emulsion has elicited delayed-type hypersensitivity reactions in patients who were immunized; and in the MDS study, 42% of immunized patients have demonstrated WT1 peptide-specific CTLs.[26]

DSP-7888 Dosing Emulsion has been well tolerated thus far. Overall, the most frequently observed AE is ISR. In one case, in a Japanese patient with MDS, this progressed to cellulitis and pyoderma gangrenosum. Of note, in the US Phase 1 study involving doses of 3.5 mg or 10.5 mg, ISRs have been of Grade 1 or 2 in intensity, easily managed, and infrequently reported. Review of the study patients with malignant glioma, both pediatric and adult, does not reveal any safety concerns specific to this population. These studies are ongoing, and additional information regarding DSP-7888 Dosing Emulsion can be found in the current Investigator's Brochure.

6.2 Rationale

Glioblastoma, with its exceedingly poor prognosis, remains a disease with a significant unmet medical need; and there remains an ongoing need for new therapies in this disease.

A high percentage of GBM tumors express WT1, and WT1 may be critical to the maintenance of the oncologic state in GBM; therefore, it is a potentially important target for the development of anti-GBM therapies. WT1 vaccines have demonstrated preliminary evidence of activity in patients with GBM, and DSP-7888 Dosing Emulsion has demonstrated safety in the doses proposed for this study. The addition of Bev may further enhance the activity of a tumor vaccine. VEGFA inhibits maturation of dendritic cells into functional cells and may also reduce the cytotoxic activity of T cells, so that inhibition by of VEGF-A may enhance these activities. In addition, Bev can decrease the levels of myeloid derived suppressor cells.[34] Therefore, Bev may create a more fertile immunological field for the activity of DSP7888 Dosing Emulsion.

DSP-7888 Dosing Emulsion given i.d. in a dose of 10.5 mg has been shown to be safe and to induce immunological responses in patients tested with this dose thus far. This dose and route of administration will therefore be employed in this study. Bev is the standard of care for patients with recurrent or progressive GBM and, therefore, represents the appropriate comparator arm.

A Phase 3 study assessed Bev plus radiotherapy or placebo in patients with glioblastoma; disease progression, OS, and quality of life were measured throughout the study. For the combination of bevacizumab with standard radiotherapy, the study did not show improved OS; however, the study results showed a trend of improved PFS. Based on the above, the approved use of Bev as a single agent in recurrent GBM, and the unmet medical need in GBM, there is an appropriate medical and scientific rationale for the combination of DSP-7888 Dosing Emulsion plus Bev in the treatment of recurrent or progressive GBM.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective is to compare the OS between treatment with DSP-7888 Dosing Emulsion plus Bev versus Bev alone in patients with recurrent or progressive GBM following initial therapy.

7.2 Key Secondary Objective

To compare the 12-month survival rate between treatment with DSP-7888 Dosing Emulsion plus Bev versus Bev alone.

7.3 Other Secondary Objectives

The other secondary objectives of the study are:

- To compare the PFS of DSP-7888 Dosing Emulsion plus Bev to Bev alone
- To compare the 6-month PFS rate of DSP-7888 Dosing Emulsion plus Bev to Bev alone
- To compare the response rate of DSP-7888 Dosing Emulsion plus Bev to Bev alone
- To compare the duration of response of DSP-7888 Dosing Emulsion plus Bev to Bev alone
- To describe the AE profile of DSP-7888 Dosing Emulsion plus Bev

7.4 Exploratory Objectives

The exploratory objectives of the study are:

- To describe the relationship between pharmacodynamic parameters such as WT1 peptide-specific CTL activity and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion plus Bev
- To describe the relationship between expression of WT1 by IHC and CISH in tumor tissue and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion plus Bev
- To collect DWI for future analysis of imaging findings and correlation with disease progression

- To characterize the NANO scale score profile post DSP-7888 Dosing Emulsion plus Bev or Bev alone

7.5 Endpoints

7.5.1 Primary Endpoint

The primary endpoint is OS and is defined as the interval between randomization and death from any cause. Patients who are lost to follow-up will be censored on the last day they were known to be alive.

7.5.2 Key Secondary Endpoint

The key secondary endpoint is the 12-month survival rate defined as the proportion of patients alive 12 months after randomization.

7.5.3 Other Secondary Endpoints

- PFS is defined as the interval between randomization and progression, determined by central radiology review, or death from any cause.
- 6-month PFS rate is defined as the proportion of patients alive at 6 months after randomization and without progressive neoplastic disease.
- The response rate is defined as the proportion of patients exhibiting a response (CR plus PR) based on the mRANO criteria as determined by the central radiology review.
- The duration of response is defined as the interval between first documented oncological response and progression of disease or death from any cause, with response based on the mRANO criteria as determined by the central radiology review.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

This study is divided into 2 parts. Part 1 is a safety lead-in phase. Part 2 is a randomized, active-controlled, multicenter, open-label, parallel-group, adaptive Phase 3 study of DSP-7888 Dosing Emulsion plus Bev versus Bev alone in patients with recurrent or progressive GBM following treatment with first line therapy consisting of surgery and radiation with or

without chemotherapy. An adaptive Phase 3 design with 2 IAs and 1 FA is employed in Part 2 of this study (Section 11.6).

Patients may have undergone a second surgery at the time of recurrence or progression but may not have received any other anti-neoplastic therapy. Patients are randomized 1:1 to treatment with DSP-7888 Dosing Emulsion plus Bev or Bev alone.

Potential study subjects first undergo pre-screening to determine appropriate HLA type due to the nature of the vaccine DSP-7888. DSP-7888 Dosing Emulsion is active in subjects with HLA-A*02:01, HLA-A*02:06, or HLA-A*24:02.

Following HLA determination, a screening phase of up to 28 days determines eligibility. Following verification of eligibility and enrollment, DSP-7888 Dosing Emulsion is administered i.d. every 7 days (± 1 day) for 5 doses (the Induction Phase); then every 14 days (± 3 days) for Doses 6 to 15 (the Consolidation Phase), and then every 28 days (± 7 days) for Doses 16 and above (the Maintenance Phase). Bev will be administered every 14 ± 3 days in the labeled dose of 10 mg/kg intravenously (i.v.).

Part 1:

In Part 1, 3 patients will be treated with the combination of DSP-7888 Dosing Emulsion plus Bev in a single-arm manner. DSP7888 Dosing Emulsion will be administered at a dose of 10.5 mg i.d. in the schedule described above and Bev will be administered at the dose and schedule described above. If 0 of these first 3 patients experiences a DLT, then the study will proceed to Part 2, which will randomize patients to the combination of DSP-7888 Dosing Emulsion plus Bev or to Bev alone.

If 1 of the first 3 patients experiences a DLT, then 3 more patients will be enrolled at the same treatment regimen. If no additional DLTs are observed at the same dose (with 1/6 DLTs), then the study will proceed to Part 2. However, if 2 or more of the first 6 patients experience a DLT, then the dose of DSP-7888 Dosing Emulsion will be decreased to 3.5 mg i.d., and an additional 3 patients will be treated with the combination of DSP-7888 Dosing Emulsion plus Bev.

If 0 of these 3 patients experiences a DLT at this reduced dose of DSP-7888 Dosing Emulsion, then the study will proceed to Part 2. If 1 of the 3 patients experiences a DLT at the reduced dose of DSP-7888 Dosing Emulsion, then 3 more patients will be enrolled at the same treatment regimen. If no additional DLTs are observed at the same dose (with 1/6 DLTs), then the study will proceed to Part 2. However, if 2 patients or more experience a DLT at this reduced dose of DSP-7888 Dosing Emulsion plus Bev, then enrollment will be placed on hold until the Sponsor decides how best to proceed.

In summary, if 0 of the first 3 patients or 1 of the first 6 patients experiences a DLT, then the study will proceed to Part 2. The MTD is decided only when 6 patients are treated at a

dose level with ≤ 1/6 DLTs. If at least 2/3 or 2/6 DLTs are observed, then the MTD has been exceeded. Dosing should stop, and the dose should be de-escalated to DSP-7888 Dosing Emulsion 3.5 mg. Then the process should be repeated at the reduced dose level of DSP-7888 Dosing Emulsion 3.5 mg.

The patients who complete Part 1 of the study will not be randomized into Part 2. Instead, they will continue to receive DSP-7888 Dosing Emulsion plus Bev and undergo the same assessments that are listed in Section 8.1.3.

Dose-limiting toxicity will be evaluated and applied during the Induction Phase of Part 1 (Day 1 through Day 29) and defined as the following AEs that are at least possibly related to the investigational agents per the Investigator and institutional guidelines:

- The occurrence of any Grade 3 or higher hematologic AE lasting more than 7 days;
- Any Grade 3 or higher non hematological AE that persists for more than 72 hours with the exceptions of transient nausea, vomiting, and diarrhea that are responding to supportive care;
- Any Grade 3 or higher allergic and/or hypersensitivity reactions; and,
- Any Grade 2 or higher autoimmune disease.

Patients who discontinue Part 1 of the study for reasons other than DLT during the Induction Phase will be replaced.

Part 2:

Based on the results of the DLT evaluation in Part 1, a 10.5 mg dose of DSP-7888 Dosing Emulsion was determined as the dose for Part 2. In Part 2, patients are stratified prior to randomization based on the extent of surgical resection in primary therapy (GTR versus not GTR) and KPS (Appendix 16.1) scores (60 through 70 versus 80 through 100).

Rescreening for patients in Part 2 is permitted for patients with laboratory values (AST, ALT, bilirubin, creatinine) that are out of range to meet eligibility and for patients requiring dexamethasone doses in excess of 4 mg/day (or equivalent) once the dose can be tapered to 4 mg/day (or equivalent) or less with stability in the judgement of the investigator.

Patients will continue to receive DSP-7888 Dosing Emulsion plus Bev or Bev alone independent of radiological assessment / progression:

1. Provided that the Investigator considers it to be safe for the patient
2. Provided that the Investigator determines that there is potential benefit for the patient

3. When the patient is willing to continue

Safety is assessed by the recording of AEs at each contact with the patient, by findings of physical and neurological examinations, and by the results of laboratory determinations; the severity of AEs or abnormal laboratory results is based on the CTCAE V4.03.

The criteria for response and progression is based on the mRANO criteria (Appendix 16.2),[35] and patients also undergo neurological assessments based on the NANO criteria (Appendix 16.3).[36]

Patients randomized to the Bev arm of the study undergo evaluations on a similar schedule as patients randomized to treatment with the combination of DSP-7888 Dosing Emulsion plus Bev.

Patients will undergo MRI and DWI at Screening; after 8, 16, and 24 weeks on study; then every 12 weeks thereafter; and at the End of Treatment (EOT) visit to assess their disease progression. Patients who are, in the opinion of the Investigator, clinically stable and in whom pseudo-progression is suspected will continue to be treated per protocol according to the treatment arm assigned and will have a second (confirmatory) scan performed 4-8 weeks later. Progressive disease may additionally be confirmed locally when available at the site by performing one of the following: single-photon emission computed tomography, perfusion MRI, MRI spectroscopy, ^{11}C methionine positron-emission tomography, or pathology from available surgical/biopsy specimens to differentiate from pseudo-progression. DWI-MRI assessment that is being provided from a central radiological review at the investigator's request will be available to help differentiate progression from pseudo-progression.

Patients who discontinue study treatment for any reason will continue to be followed up for efficacy (mRANO, NANO, KPS, etc.) until new treatment is commenced.

All patients will be followed up for OS, regardless of potential subsequent therapy.

Patients' immunological responses to DSP-7888 Dosing Emulsion will be measured by a variety of assays including:

- Measurement of WT1 peptide-specific CTL induction activity at various times using peripheral blood mononuclear cells of patients
- Retrospective analysis of additional biomarkers from peripheral blood and archival tumor samples

Formalin-fixed, paraffin-embedded archival tumor samples will be tested for expression of WT1 by IHC and CISH and compared to a variety of clinical outcomes in exploratory analyses. Additional exploratory analyses will evaluate the role of DWI (conducted by

central radiology review) in predicting and diagnosing true progression of neoplastic disease in patients with GBM. Exploratory analyses will be performed to investigate the relationship between the activity of DSP-7888 Dosing Emulsion and other HLA Class 1 haplotypes (A and B locus) as well as HLA Class 2.

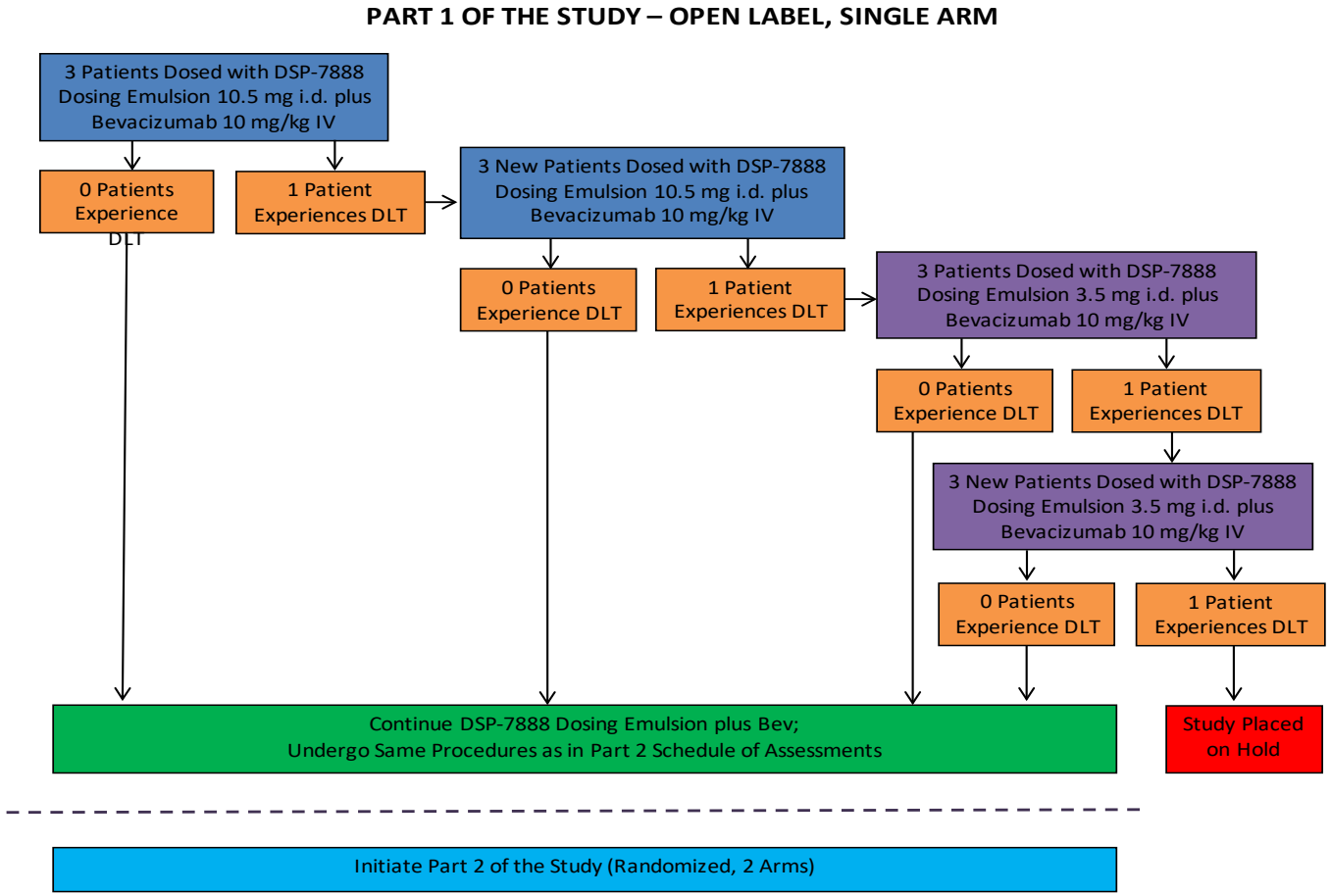
Companion diagnostics of HLA typing will be developed as part of this study.

The study duration for individual patients commences at date of pre-screening consent and completes at the date of End of Study visit. The study may be terminated early for either efficacy or futility at IA1 and for efficacy only at IA2. The study will continue until the target number of events is observed.

A flow chart of Part 1 of the study is presented in Figure 1 (Section 8.1.1); a schema of the study is presented in Figure 2 (Section 8.1.2.); and a schedule of assessments is presented in Section 8.1.3.

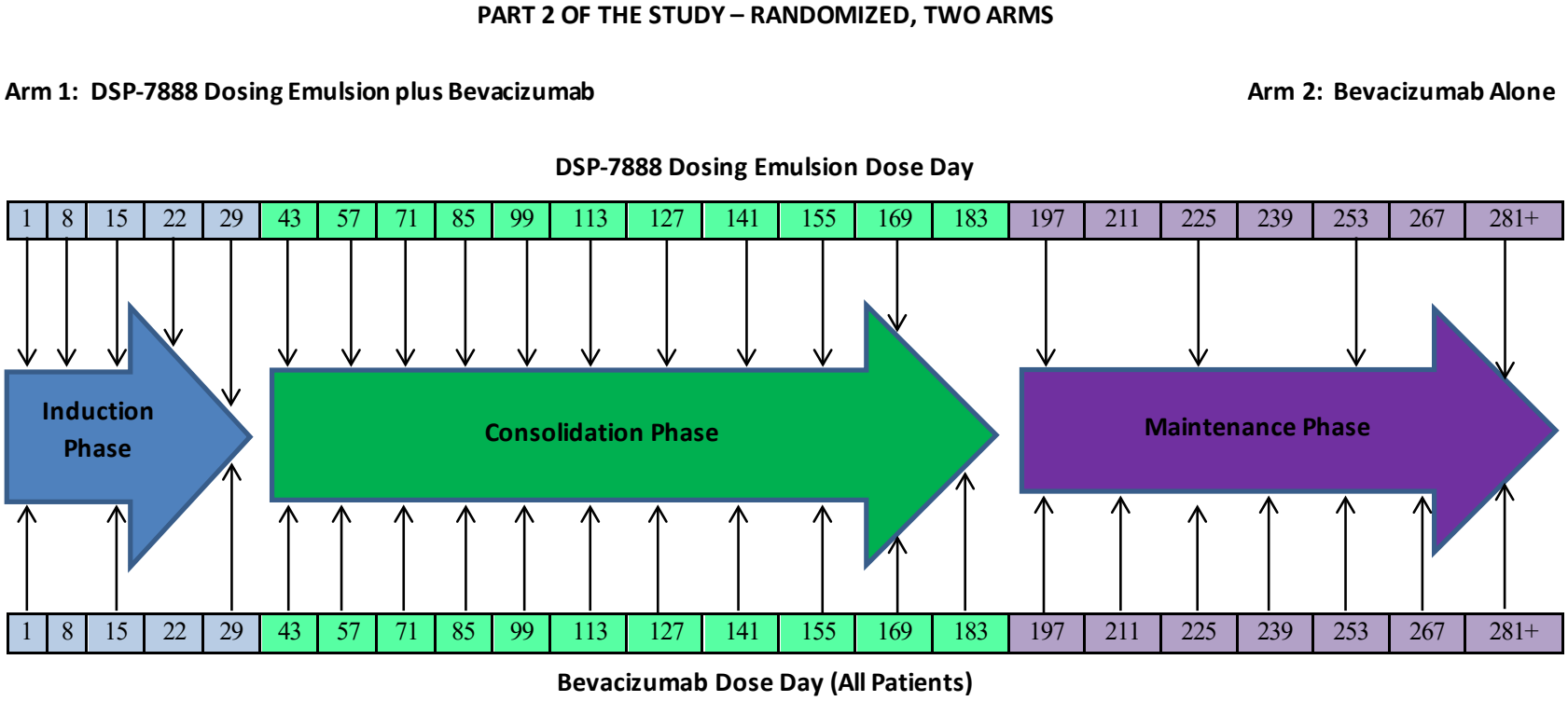
8.1.1 Flow Chart for Part 1 of the Study

Figure 1: Part 1 Flow Chart



8.1.2 Study Design for Part 2 of the Study

Figure 2: Part 2 Study Design



8.1.3 Schedule of Assessments

Procedures and Assessments	Pre-Screening	Screening	Induction Phase					Consolidation Phase											Maintenance Phase							EOT[v]	EOT F/U[w,x]
Day		-28 to -1	1	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239	253	267	>281		
DSP-7888 Dosing Emulsion[a]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		
Dose #			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		16		17		18		19		
Bev[b]			X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Informed Consent[c]	X[m]	X[n,s]																									
Demographic Information	X																										
Medical History[d]	X	X																									
Vital Signs[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination		X					X		X		X		X		X		X		X		X		X		X	X	
Neurological Examination[f]		X					X		X		X		X		X		X		X		X		X		X	X	X[x]
Karnofsky Performance Status Score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X[x]
ECG		X							X		X		X		X		X									X	
CBC[g]		X	X		X		X		X		X		X		X		X		X		X		X		X	X	
Coagulation Parameters[h]		X																									
Serum Chemistry Tests[i]		X	X		X		X		X		X		X		X		X		X		X		X		X	X	
Urinalysis[j]		X	X		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	
Pregnancy Test[k]		X																									X
Serology for HIV, Hep B, Hep C[l]		X																									
HLA Typing[m]	X[m]																										
Fresh/Archival Tumor Sample[n]		X																								X	
Companion Diagnostics Sample[o]	X																										

Procedures and Assessments	Pre-Screening	Screening	Induction Phase					Consolidation Phase											Maintenance Phase							EOT[v]	EOT F/U[w,x]
Day		-28 to -1	1	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239	253	267	>281		
DWI, Conventional MRI, and mRANO[p]		X							X				X				X						X		X	X	X[x]
IDH 1/2 mutation and MGMT Promotor Methylation Status[q]		X																									
Adverse Event and Serious Adverse Event Reporting		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Samples for CTL Induction[r,s]		X			X		X		X		X		X				X						X		X	X	
Blood Samples for Retrospective Biomarker Analyses[r,t]		X			X		X		X		X		X				X						X		X	X	
Blood Samples for Additional HLA Haplotypes				X[u]																							
Echocardiogram or MUGA		X																									
Pulse Oximetry		X																									

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bev = bevacizumab; CBC = complete blood count; CTL = cytotoxic T lymphocyte; DWI = diffusion-weighted imaging; ECG = electrocardiogram; EOT = End of Treatment; F/U = follow up; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IDH = isocitrate dehydrogenase; IHC = immunohistochemistry; INR = partial thromboplastin time; MGMT = O^6-methyl-guanyl-methyl-transferase; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; NANO = Neurological Assessment in Neuro-Oncology; PTT = partial thromboplastin time; mRANO = Modified Response Assessment in Neuro-Oncology; WBC = white blood cell.

Note 1: The windows for assessments are every 7 ± 1 day for Doses 1 to 5, every 14 ± 3 days for Doses 6 to 15, and every 28 ± 7 days for Doses 16 and above except for MRI procedures, which have an assessment window of ± 7 days around the scheduled visit day.

[a] DSP-7888 Dosing Emulsion will be administered i.d. every 7 ± 1 day for Doses 1 to 5, every 14 ± 3 days for Doses 6 to 15, and every 28 ± 7 days for Doses 16 and above.

[b] Bev will be administered intravenously every 14 ± 3 days at the labeled dose of 10 mg/kg.

[c] Informed consent must be obtained before performing any study-related procedures.

[d] Pertinent medical history will be taken during the screening phase. Prior cancer therapy data will be collected during the pre-screening phase.

[e] Vital signs will include systolic and diastolic blood pressures, pulse, respiratory rate, temperature, and weight.

[f] Neurological examination will be based on NANO criteria.
[g] CBC will include determinations of hemoglobin, hematocrit, red blood cell, WBC, WBC differential, and platelet count.*
[h] Coagulation parameters will include INR and PTT.*
[i] Chemistry tests will include determinations of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, total protein, albumin, calcium, magnesium, and phosphorous.*
[j] Urinalysis includes pH; specific gravity; dipstick determinations of glucose, ketones, protein, blood or hemoglobin, and total bilirubin. Microscopic examination must be performed for dipstick determinations of 2+ or greater. A 24-hour urine for total protein must be collected and performed for a protein dipstick result of 2+ or greater.*
[k] Pregnancy may be determined via serum or urine test.*
[l] Serology will include HIV antibody, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C virus antibody tests.*
* Although local laboratory results are permitted for treatment-related decisions, baseline eligibility will be based on the central laboratory results.
[m] HLA serotyping may be performed prior to Screening after obtaining pre-screening informed consent for HLA typing. All HLA typing is to be performed in a central laboratory.
[n] Tumor tissue will be collected (1) for WT1 by IHC and CISH, and (2) for retrospective analysis of biomarkers. (1) For WT1 by IHC and CISH: Tumor tissue samples must be collected at Screening when available. Provision of tumor tissue is preferred but not mandatory to be eligible for the study.
(2) For Retrospective Biomarker analysis: Additional informed consent will be needed from the patients prior to collection of samples, that they consent to some of their tumor tissue and additional blood samples will be used to test for as yet unspecified biomarkers (this is an optional part of the study). As these biomarkers are currently not determined, long-term storage of these samples will be required. Patients should also give additional consent to this long-term storage.
WT1 by IHC and CISH will be performed even if the WT1 expression data are available from medical records.
After the last dose of study medication, if the patient is undergoing required medical procedures that would permit retrieval of tumor tissue, a sample of this tissue is requested (but not mandatory). Additional informed consent is needed prior to collection of tumor tissue samples after the last dose of study medication at Screening.
[o] Blood samples will be collected at the same time as those for HLA typing from all the patients who undergo Pre-Screening.
[p] DWI-MRI, conventional MRI, and mRANO tumor assessments will be performed at Screening; after 8, 16, and 24 weeks on study; and then every 12 weeks thereafter. Conventional MRI should be used for mRANO assessments at the clinical sites. DWI-MRI as well as conventional MRI should be provided to the central radiology review.
[q] The analysis will be conducted only when the information is not available at enrollment.
[r] If blood is not collected at Screening, it may be obtained on Day 1 PRIOR to administration of protocol therapy. In the Maintenance Phase, blood samples should be obtained at Day 253 and then every 12 weeks thereafter.
[s] Some aliquots of the CTL blood samples may be used to investigate other HLA Class 1 haplotypes in relation to DSP-7888 activities rather than separate samples being taken from the patient.
[t] Additional informed consent is needed prior to the collection of blood samples for retrospective biomarker analyses.
[u] Blood will be collected from the DSP-7888 Dosing Emulsion plus Bev arm on C1D8. If this sample is not collected on this cycle day, then it should be collected at the next cycle visit.
[v] The EOT visit should occur within 28 days of the end of treatment, and prior to the initiation of any new post-study treatment.

[w] Patients who discontinue treatment for PD and are treated with an alternative therapy should be followed up for survival (using direct methods [ie, telephone call or email to patient/patients' relatives] or indirect methods [ie, medical record review or obituary listing review]) and post-treatment and anti-tumoral therapy every 3 months and/or on an ad hoc basis for safety or regulatory purposes, or a prespecified analysis; females of childbearing potential and female partners of male patients should be followed up for up to 90 days to ensure no pregnancy occurs.
[x] All other patients who discontinue treatment (including patients who discontinue treatment for PD and who will not receive further treatment, or where the Investigator believes it in the patient's best interest to discontinue treatment), should be followed up for survival (using direct or indirect methods) and post-treatment and anti-tumoral therapy every 3 months and/or on an ad hoc basis for safety or regulatory purposes, or a prespecified analysis. In addition: KPS, NANO criteria assessment, DWI-MRI, conventional MRI, mRANO assessment of response, and documentation of corticosteroid usage for mRANO assessment, should be performed on Day 57 ± 14 days, Day 113 ± 14 days and Day 169 ± 14 days, if withdrawal of study treatment occurs prior to these timepoints and until the patient receives further treatment for GBM; and, females of childbearing potential and female partners of male patients, should be followed up for up to 90 days to ensure no pregnancy occurs.

8.2 Selection of Study Population

8.2.1 Number of Planned Patients

Between 3 and 12 patients were to be enrolled in Part 1 of the study (Section 8.1.1). As of Protocol Amendment 7, 4 patients had been enrolled into Part 1 of the study.

Part 2 is an adaptive Phase 3 study in which approximately 215 to 480 patients with GBM will be enrolled from approximately 70 investigational sites in the US, Canada, Japan, Taiwan, and South Korea.

Note that Part 2 of the study is an event-driven adaptive trial and statistical power of Part 2 of the study is determined by the target number of death events instead of the number of patients. The actual number of randomized patients in Part 2 may vary to observe the targeted number of OS events, depending on the outcome of the IAs, the duration of the study and operational feasibility of the trial. Details of statistical power, event number and sample size are provided in Section 11.2.1.

8.2.2 Inclusion Criteria

The study will enroll patients with GBM whose tumors have recurred or progressed following initial treatment with surgery, radiation, and chemotherapy. To be eligible for study entry, patients must satisfy all of the following criteria:

Note: The latest laboratory value should be used to determine eligibility if the laboratory tests are performed more than once during the Screening phase. Eligibility will always be determined by the results from the central laboratory.

1. Patients or their legal representatives must be able to provide written informed consent.

2. Histologically confirmed diagnosis of supratentorial GBM (Grade 4 astrocytoma).

3. Radiographic evidence of first recurrence or progression of GBM following primary therapy consisting of surgery (biopsy or resection) and radiation with or without chemotherapy; patients may have undergone a second debulking surgery following initial recurrence or progression. Patients whose tumors are O^6-methyl-guanyl-methyl-transferase (MGMT) methylated-promoter negative need not have received chemotherapy in the past to be eligible.

4. Human leukocyte antigen (HLA) type HLA-A*02:01, HLA-A*02:06, or HLA-A*24:02.

5. Age ≥ 18.

6. Karnofsky Performance Status (KPS) score of ≥ 60.

7. Serum creatinine value < 2X the upper limit of normal (ULN) for the reference laboratory.

8. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3X the ULN and total bilirubin < 2X the ULN for the reference laboratory.

9. Men and women of childbearing potential must agree to use a reliable method of contraception (oral contraceptives, implantable hormonal contraceptives, or double barrier method) or agree to completely refrain from heterosexual intercourse for the duration of the study and for 180 days following the last dose of DSP-7888 Dosing Emulsion.

10. Patients must have recovered from the effect of all prior therapy to Grade 2 or less.

11. Patients must be at least 28 days from any major surgery, and any surgery incisions or wounds must be completely healed.

12. Patients must be at least 12 weeks from the completion of prior RT in order to discriminate pseudo-progression of disease from progression.

13. Patients must be at least 4 weeks from the completion of prior systemic or intracranial chemotherapy.

14. Patients must stop Novo-TTF treatment one day prior to study therapy (no washout period is needed). However, any wounds from TTF must be adequately healed per Inclusion Criterion #11.

15. For patients who are not receiving therapeutic anticoagulation treatment, an international normalized ratio (INR) and a partial thromboplastin time (PTT) ≤ 1.5 × the ULN; patients who are receiving anticoagulation treatment should be on a stable dose.

16. Patient's left ventricular ejection fraction (LVEF) > 40%.

17. Patient has a resting pulse oximetry of 90% or higher.

8.2.3 Exclusion Criteria

Patients will be excluded from the study if one or more of the following criteria are applicable:

1. Prior therapy with Bev.

2. Patients with secondary GBM.

3. Any anti-neoplastic therapy, including RT or laser interstitial thermal therapy, for first relapse or recurrence.

4. Evidence of leptomeningeal spread (gliomatous meningitis) of tumor or any history, presence, or suspicion of metastatic disease extracranially.

5. Evidence of impending herniation on imaging.

6. Has known multifocal disease. Multifocal disease is defined as discrete sites of disease without contiguous T2/FLAIR abnormality that require distinct radiotherapy ports. Satellite lesions that are associated with a contiguous area of T2/FLAIR abnormality as the main lesion(s) and that are encompassed within the same radiotherapy port as the main lesion(s) are permitted.

7. Patients with infections that have required treatment with systemic antibiotics within 7 days prior to the first dose of protocol therapy.

8. The need for systemic glucocorticoids in doses in excess of 4 mg/day of dexamethasone or in comparable doses with other glucocorticoids.

9. Treatment with any investigational agents within 5 half-lives of the agent in question or, if the half-life is unknown, within 28 days of enrollment.

10. Pregnant or lactating females.

11. Prior history of malignancy within 3 years of enrollment other than basal or squamous cell carcinoma of the skin, cervical intra-epithelial neoplasia, in situ carcinoma of the breast, or localized prostate cancer treated with surgery or RT with a prostate specific antigen of <0.01 ng/mL.

12. Patients with active autoimmune diseases within 2 years of enrollment into the study including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, Wegener's granulomatosis, ulcerative colitis, Crohn's disease, myasthenia gravis, Graves' disease, or uveitis except for psoriasis not requiring systemic therapy, vitiligo or alopecia areata, or hypothyroidism; if an autoimmune condition has been clinically silent for 12 months or greater, the patient may be eligible for enrollment.

13. Patients on immunosuppressive therapies; the use of topical, inhalational, ophthalmologic, or intra-articular glucocorticoids or the use of physiologic replacement doses of glucocorticoids is permitted.

14. Patients with primary immunodeficiency diseases.

15. Patients with significant bleeding in the preceding 6 months prior to study enrollment or with known coagulopathies.

16. History of abdominal fistula, intestinal perforation, or intra-abdominal abscess in the preceding 12 months prior to study enrollment.

17. Positive serology for human immunodeficiency virus (HIV) infection, active hepatitis B*, or untreated hepatitis C; patients who have completed a course of anti-viral treatment for hepatitis C are eligible.

    *In cases of negative results for HepB surface antigen with positive HepB core antibody, HBV DNA testing is required.

18. Patient has a medical history of frequent ventricular ectopy, e.g., non-sustained ventricular tachycardia (VT).

19. Significant cardiovascular disease, including New York Hospital Association Class III or IV congestive heart failure, myocardial infarction within 6 months of study enrollment, unstable angina, poorly controlled cardiac arrhythmias, or stroke in the preceding 6 months prior to study enrollment.

20. Any other uncontrolled inter-current medical condition, including systemic fungal, bacterial, or viral infection; uncontrolled hypertension; diabetes mellitus; or chronic obstructive pulmonary disease requiring 2 or more hospitalizations in the preceding 12 months prior to study enrollment.

21. Any psychiatric condition, substance abuse disorder, or social situation that would interfere with a patient's cooperation with the requirements of the study.

22. Known sensitivity to Bev or any of the components of DSP-7888 Dosing Emulsion.

23. Patient has a QTcF (QT corrected based on Fridericia's equation) interval > 480 msec (CTCAE = Grade 2) or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) at screening. (Patients with bundle branch block and a prolonged QTc interval should be reviewed by the Medical Monitor for potential inclusion.)

24. Patient has dyspnea at rest (CTCAE ≥ Grade 3) or has required supplemental oxygen within 2 weeks of study enrollment.

8.2.4 Reasons for Discontinuation of Protocol Therapy

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Withdrawal of partial consent means that the patient does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent study visits or procedures). Patients may decline to continue receiving investigational product at any time during the study. These patients, as well as those who have stopped receiving investigational product for other reasons (eg, Investigator or Sponsor concern) should continue the schedule of study observations.

Rescreening for patients in Part 2 will be permitted for patients with laboratory values (AST, ALT, bilirubin, creatinine) that were out of range to meet eligibility and for patients requiring dexamethasone doses in excess of 4 mg/day (or equivalent) once the dose can be tapered to 4 mg/day (or equivalent) or less with stability in the judgement of the investigator.

Patients will continue to receive DSP-7888 Dosing Emulsion plus Bev or Bev alone independent of radiological assessment / progression:

1. Provided that the Investigator considers it to be safe for the patient
2. Provided that the Investigator determines that there is potential benefit for the patient
3. When the patient is willing to continue

Patients will be discontinued from protocol therapy for any of the following reasons:

- The need for a prohibited treatment for a concomitant illness or AE
- An AE that precludes further administration of DSP-7888 Dosing Emulsion or Bev (see Section 8.3.2.1)
- Patient withdraws consent for continued administration of DSP-7888 Dosing Emulsion or Bev
- The Investigator believes it is in the patient's best interest to discontinue protocol therapy or to initiate alternative treatment for GBM
- Pregnancy
- Lost to follow-up (3 attempts to contact the patient must be made by the investigative site by phone or email before a patient is considered lost to follow-up)
- Patient moves out of the Investigator's catchment area or is unable to continue to come to the investigational site

8.2.5 Reasons for Discontinuation from the Clinical Study

Reasons for discontinuation from the study include:

- Patient withdraws consent for continued participation
- Lost to follow-up
- Death of the patient
- The Sponsor deems it necessary to discontinue the study

Withdrawal of full consent for a study means that the patient does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any patient may withdraw full consent to participate in the study at any time during the study. The Investigator will discuss with the patient the most appropriate way to withdraw to ensure the patient's health.

Patients who do not comply with the protocol or who withdraw consent during the Induction Phase in Part 1 of the study will be replaced. Patients who stop study drug for any other reason during Part 1 will not be replaced. No patients will be replaced during Part 2 of the clinical study. Patients are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the patient's chart and in the electronic case report form (eCRF).

Patients withdrawing from the study will be encouraged to complete the same final evaluations as patients completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for patients who complete the study.

Reasonable efforts will be made to contact patients who are lost to follow-up. These efforts must be documented in the patient's file.

The Sponsor has the right to terminate the study at any time in the case of serious adverse events (SAEs) or if special circumstances concerning the investigational product or the company itself occurs, making further treatment of patients impossible. In this event, the Investigator(s) will be informed of the reason for study termination.

Full details will be recorded on the withdrawal page of the eCRF.

8.3 Investigational Products

8.3.1 Identity of Investigational Products

8.3.1.1 DSP-7888 Dosing Emulsion

DSP-7888 Dosing Emulsion will be administered at the study site by staff trained in the administration of intradermal drugs. Patients will be treated with a dose of 10.5 mg (6.0 mg DSP-7888-K plus 4.5 mg DSP-7888-H) administered in 6 x 100 µL intradermal injections (Table 1) in the following schedule:

- Induction Phase: once every 7 ± 1 days (Doses 1 through 5)
- Consolidation Phase: once every 14 ± 3 days (Doses 6 through 15)
- Maintenance Phase: once every 28 ± 7 days until discontinuation (Dose 16 and thereafter)

Table 1 DSP-7888 Dosing Administration

Administration Route	Dose Level	Number of Injection Sites	Amount per Injection SITE (mL)	Total Amount to Administer per Dosing DAY (mL)
Intradermal	10.5 mg	6	0.1	0.6

In the event of a DLT occurring during Part 1 of the study, the patient should be permanently removed from study treatment and should not be replaced. In the event of a study drug-related AE occurring in Part 2 of the study, the dose modification criteria should be applied by the Investigator.

Wherever possible, the posterior neck and posterior shoulder regions should be used primarily as injection sites with other areas surrounding regional lymph nodes in the upper arm, the lower abdomen, or the femoral area used if additional dosing sites are required. To the extent possible, injections of study drug should be administered to separate parts of the body and separated from one another. Rotation of injection sites is permitted. Injection sites should not be chosen in the areas of any ongoing skin condition (eg, an area of psoriasis).

A full description of DSP-7888 Dosing Emulsion preparation can be found in the Study Pharmacy Manual.

8.3.1.2 Bevacizumab

Bev will be administered in a dose of 10 mg/kg by i.v. infusion every 14 ± 3 days. The first infusion will be administered over 90 minutes; the second infusion may be administered over 60 minutes if the first infusion was well tolerated; and subsequent infusions may be administered over 30 minutes if the second infusion was well tolerated. Additional information regarding Bev administration may be found in the AVASTIN® Full Prescribing Information or other local product information. On the days when both DSP-7888 Dosing Emulsion and Bev are administered, DSP-7888 Dosing Emulsion should be administered first. Bev will be obtained by the clinical site, except in South Korea where different regulations apply.

8.3.2 Dose Delay, Dose Reduction, and Study Stopping Criteria

8.3.2.1 DSP-7888 Dosing Emulsion

Part 1: This part of the study is a safety run-in cohort to determine the RD for Part 2. The dose of DSP-7888 Dosing Emulsion is 10.5 mg. Bev will be administered at a dose of 10 mg/kg by i.v. infusion.

Any patient who experiences a DLT with DSP-7888 Dosing Emulsion should be permanently removed from the study treatment and should not be replaced.

Note: The dose of DSP-7888 Dosing Emulsion may be reduced for individual patients to 3.5 mg or 1.75 mg if any dose reduction criterion is met.

Part 2: Based on the results of the DLT evaluation in Part 1, a 10.5 mg dose of DSP-7888 Dosing Emulsion was determined as the dose for Part 2. Bev is administered at a dose of 10 mg/kg by i.v. infusion.

Note: The dose may be reduced for individual patients to 3.5 mg or 1.75 mg of DSP-7888 Dosing Emulsion if any dose reduction criterion is met.

The dose of DSP-7888 Dosing Emulsion should be held for any Grade 3 or Grade 4 toxicity that is at least possibly related to DSP-7888 Dosing Emulsion, but that is not a DLT, with the exception of Grade 3 ISRs which do not require hospitalization, where patients may continue on DSP-7888 Dosing Emulsion without holding or reducing the dose per Investigator's judgment on a case-by-case basis, after consultation with the Sponsor. Dosing may be resumed at a reduced dose once the toxicity has reverted to Grade 2 or less. Treatment with Bev may be put on hold in case of Grade 3 or higher ISR, to avoid any delay in wound healing.

For Grade 2 toxicity at least possibly related to DSP-7888 Dosing Emulsion, dosing may take place at a reduced dose according to Table 2 below. On days when DSP-7888 Dosing Emulsion is held for toxicity, Bev should be administered if scheduled for that

day. If toxicities related to DSP-7888 Dosing Emulsion preclude administration of DSP-7888 Dosing Emulsion for 4 consecutive treatments, DSP-7888 Dosing Emulsion should be discontinued with continuation of Bev alone. However, if in the opinion of the Investigator the patient is clinically stable and receiving benefit from study drug, the patient may restart treatment with DSP-7888 Dosing Emulsion on a case-by-case basis, after consultation with the Sponsor.

Dose reduction should be undertaken as shown in Table 2 and Table 3:

Table 2 Dose Reduction Schedule

Starting Dose Level		Reduced Dose Level		
Starting Dose Level	# Injection Sites x Volume/Site	Strategy	Dose	# Injection Sites x Volume/Site
10.5 mg	6 x 100 µL	Dose Reduction	3.5 mg	2 x 100 µL
3.5 mg	2 x 100 µL	Dose Reduction	1.75 mg	2 x 50 µL

Note: A dose increase is not allowed after dose reduction. A 2-step dose reduction is allowed.

Table 3 Dose Reduction Administration

Administration Route	**Dose Level**	**Number of Injection Sites**	**Amount per injection site (mL)**	**Total Amount to administer per dosing day (mL)**
Intradermal	3.5 mg	2	0.1	0.2
Intradermal	1.75 mg	2	0.05 (50 µL)	0.1

After the Induction Phase, dose reduction is permitted due to ISRs if the Investigator or Sub-Investigator has judged that a dose reduction is medically required.

Patients who experience Grade 3 or higher toxicities at a dose of 1.75 mg that are at least possibly related to DSP-7888 Dosing Emulsion will be removed from the protocol therapy, with the exception of patients with Grade 3 ISRs assessed as at least possibly related to DSP-7888 Dosing Emulsion not requiring hospitalization; these patients may continue on DSP-7888 Dosing Emulsion per Investigator's judgment on a case-by-case basis, after consultation with the Sponsor.

8.3.2.2 Bevacizumab

Bev toxicities should be managed according to the Full Prescribing Information or other local product information. There are no dose reductions for Bev. Treatment with Bev may be put on hold for Grade 3 or higher ulceration of injection sites due to DSP-7888 Dosing Emulsion. If a toxicity felt to be associated with Bev requires temporary discontinuation of Bev, DSP-7888 Dosing Emulsion will continue to be administered on schedule. If toxicities related to Bev preclude administration of Bev for 6 consecutive weeks (3 treatment cycles of Bev), then Bev should be permanently discontinued. For patients on the Bev alone arm, this will constitute discontinuation of protocol therapy. For patients randomized to the combination arm, treatment will continue with DSP-7888 Dosing Emulsion alone.

8.3.2.3 Treatment of Injection Site Reactions

Injection site reactions will be graded according to the following criteria (Table 4). The symptoms that occur with injection site reaction should be reported as "injection site reaction" (not described as "erythema," "itching," etc.).

Table 4 Grading of Injection Site Reactions

Grade 1	Grade 2	Grade 3	Grade 4
Tenderness, erythema, warmth, pruritus, swelling	Pain, induration, fatty degeneration, edema, phlebitis	Ulcer, necrosis, abscess, erosion, or severe tissue injury, requiring surgical intervention or skin graft	Life-threatening, required emergency care
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]	Life-threatening consequences; urgent intervention indicated

ADL = Activities of Daily Living.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Factors other than the appearance of the ISR should be taken into consideration when evaluating the severity of an ISR. A pinpoint ulcer, for example, may not truly be indicative of a Grade 3 ISR, and other factors, such as the presence of fever, or the need for systemic analgesia, should also be considered in determining ISR severity and guiding decisions regarding discontinuation of DSP-7888 Dosing Emulsion.

8.3.3 Grade 1 Injection Site Reactions

Irrigation with physiological saline is recommended. Topical steroids should be applied as appropriate. A mid-strength Class 4 topical steroid is recommended (National Psoriasis Foundation, 1996-2016). Examples include:

- Flurandrenolide ointment, 0.05%
- Mometasone furoate cream, 0.1%
- Triamcinolone acetonide cream/spray, 0.1%
- Fluocinolone acetonide ointment, 0.03%
- Desoximetasone cream or ointment, 0.05%
- Hydrocortisone valerate ointment, 0.2%

Antiseptics that are susceptible to immunization should not be used.

Application of topical antibiotics is not recommended, as it may worsen the reaction. However, the antibiotics may be used in the presence of infectious findings or positive culture results.

8.3.4 Grade 2/3 Injection Site Reactions

- In the presence of a Grade 2 ISR, the administration of DSP-7888 Dosing Emulsion may continue at a reduced dose of 3.5 mg (2.0 mg killer peptide plus 1.5 mg helper peptide). Further dose reduction to 1.75 mg as described above is permitted.
- DSP-7888 Dosing Emulsion should be held in the presence of a Grade 3 ISR requiring hospitalization (as described above); once the ISR resolves to Grade 2 or less, administration of DSP-7888 Dosing Emulsion may resume at a reduced dose of 3.5 mg (2.0 mg killer peptide plus 1.5 mg helper peptide). Further dose reduction to 1.75 mg as described above is permitted.
- Irrigation with physiological saline and use of topical steroids as described for Grade 1 ISRs above should be instituted.

- If an abscess forms, incision and drainage should be carried out to avoid exacerbation of the inflammatory response around the site. After the drainage, the site should be washed with physiological saline followed by application of topical steroids as appropriate. Most abscesses should be sterile, but cultures should be obtained.

- Topical antibiotics should not be used unless cultures indicate infection.

- Open areas may be protected with a non-stick dressing.

If severe ISRs are observed, local (subcutaneous) injection of steroids may be considered.

8.3.5 Study Stopping Rules

The Sponsor will promptly review all serious life-threatening and fatal events (other than death due to disease progression) reported in the study and perform a causality assessment.

Based on the causality assessment of life-threatening and fatal events that occur from the start of treatment with DSP-7888 Dosing Emulsion and up to 30 days from the last dose of DSP-7888 Dosing Emulsion (other than death due to disease progression), the Sponsor will determine whether the study will be suspended for safety review.

The Sponsor will determine whether the study will be modified, continue enrollment or be terminated based on the following scenarios:

- Any cases of death (other than death related to progressive disease) that occur from the start of treatment with DSP-7888 Dosing Emulsion and up to 30 days from the last DSP-7888 Dosing Emulsion administration and deemed by the Sponsor to be related to any of the study's drugs.
- If the percentage of patients presenting with drug-related (assessed by Sponsor) Grade 4 or higher AE within a particular medical concept (eg, hypersensitivity) in this study is higher than that reported in patients treated with DSP-7888 Dosing Emulsion within the clinical program and as reported in the literature for GBM patients.

The causality assessment and safety reviews will occur in the context of the Sponsor's safety governance processes including the study team and senior leadership. As part of the safety review, in addition to ongoing routine review of the safety data by the IDMC, the Sponsor may choose to consult with the IDMC on an ad hoc basis.

Based on the safety review, the Sponsor will determine whether the study may continue (with or without a protocol amendment) or if it must be terminated.

8.3.6 Packaging and Labeling

Sumitomo Dainippon Pharma Oncology, Inc. (SDP Oncology) will supply the bulk product. The study packaging will be performed by a contract manufacturing organization (Almac) designated by Syneos (with Sponsor oversight) and SDP Oncology. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

8.3.7 Method of Assigning Patients to Treatment Groups

The study will be divided into 2 parts. Part 1 will be a non-randomized, open-label Induction Phase where all patients will be treated with the combination of DSP-7888 Dosing Emulsion plus Bev in a single-arm manner. The objective of Part 1 is to establish the safety of the combination of DSP-7888 Dosing Emulsion plus Bev. Patients who discontinue Part 1 of the study for reasons other than DLT during the Induction Phase will be replaced.

Once the safety of the combination of DSP-7888 Dosing Emulsion plus Bev has been established, Part 2 (the randomized part of the study) will begin. In Part 2, patients will be stratified prior to randomization based on the extent of surgical resection in primary therapy (GTR versus not GTR) and KPS class (60 through 70 versus 80 through 100) and will be randomized in a 1:1 ratio for DSP7888 Dosing Emulsion plus Bev or Bev alone via the Endpoint Interactive Voice/Web Response System. The treatment assignment is to be obtained in Part 2 after the study patient has passed all inclusion and exclusion criteria and has been enrolled in the study prior to the initiation of the study treatment or first dosing visit. Withdrawn patients will not be replaced in Part 2 of the study.

8.3.8 Selection of Doses in the Study

DSP-7888 Dosing Emulsion has been evaluated in 2 doses in clinical studies in Japan and was evaluated in a Phase 1 study in the US. Doses of 3.5 mg and 10.5 mg have been well tolerated in both Japanese and US study patients with little difference in the overall safety profiles of both doses observed to date. Induction of cytotoxic T cell activity may occur more rapidly following the 10.5 mg dose, and so this dose was selected for investigation in this study.

In Part 1 of study DSP-7888-201G, no DLTs were observed with 10.5 mg DSP-7888 Dosing Emulsion, therefore, Part 2 proceeded with a dose of 10.5 mg DSP-7888 Dosing Emulsion i.d.

The dose of Bev, 10 mg/kg i.v. every 14 days, is the currently approved dose for the treatment of recurrent GBM.

8.3.9 Prior and Concomitant Therapy

The study will enroll patients with GBM whose tumors have recurred or progressed following initial treatment with surgery, radiation, and chemotherapy

Patients should receive treatment for all inter-current medical conditions or AEs at the discretion of the Investigator in conformance with community or institutional medical standards.

Patients may also receive anti-seizure medications and symptomatic treatments (e.g., analgesics, anxiolytics, and hypnotics) at the discretion of the Investigator.

Patients may occasionally require systemic glucocorticoids of 4 mg/day of dexamethasone or equivalent for other glucocorticoids at the discretion of the Investigator to treat changes in neurological status; DSP-7888 Dosing Emulsion administration should continue at the discretion/judgement of the investigator while the patient is receiving corticosteroid treatment. Efforts must be made to taper any systemic glucocorticoids to doses of less than 4 mg/day of dexamethasone (or equivalent doses of other glucocorticoids per Appendix 16.4) as soon as possible; topical, inhalational, ophthalmologic, intra-articular, and replacement doses of glucocorticoids are permitted. If a patient requires doses of corticosteroids in excess of dexamethasone 4 mg/day (or equivalent) to manage neurological symptoms, please contact the medical monitor for discussion/approval.

Patients with CTCAE ≥ 2 with hypomagnesemia (magnesium < 0.5 mmol/L) and/or hypokalemia (potassium < the lower limit of normal [LLN] - 3.0 mmol/L) should receive electrolyte supplementation.

8.3.9.1 Prohibited Medication/Therapy

- Patients may not receive any therapy directed at GBM including RT.
- Patients may not receive cytotoxic agents, hormonal agents for anti-tumoral therapy, monoclonal antibodies, immunomodulatory agents, or investigational agents during the study.
- Patients may not receive any immunosuppressive agents other than glucocorticoids as described in Section 8.3.9.
- Patients should not receive live vaccines (eg, Flu-Mist®); vaccines containing killed organisms are permitted.

8.3.9.2 Permitted Medication/Therapy

Patients on the study will be permitted to receive COVID-19 vaccinations that are authorized for use by the health authorities of the specific country or region; this should be discussed as necessary with the Medical Monitor on a case-by-case basis. For additional information refer to NCCN guidance.[37]

8.3.10 Treatment Compliance

The administration of investigational product will occur at the clinical site; therefore, the study staff will be able to confirm compliance.

8.3.11 Blinding

This is an open-label study. The primary endpoint of Part 2 of this study is OS, the assessment of which is unlikely impacted by the open-label nature of the study.

To comply with ICH E6 (R2) Guideline for Good Clinical Practice (2016), which recommends the blinded review of planned analyses, and to minimize the risk of potential bias into interim and final analyses for the adaptive Phase 3 design in Part 2, blinding controls have been implemented on the aggregate data by treatment arm. Specifically, the IA results will be reviewed by the IDMC and will only be available to the IDMC and selected unblinded team members. The investigators, the patients, the Sponsor and CRO study personnel who interact with the site and other blinded partners do not have access to the IA results.

9 STUDY PROCEDURES

9.1 Timing of Study Procedures

Patients will provide written informed consent before any study-related procedures are performed.

The planned study assessments are in Section 8.1.3.

9.1.1 Pre-Screening Phase

Prior to the Screening Phase, the following activities will occur:

- Record demographic data, such as ethnic origin, date of birth, and sex.
- Perform HLA typing for subtype to determine the patient's eligibility for the study.

- Collect blood for companion diagnostic development (blood samples will be collected at the same time as those for HLA typing).
- Collect prior cancer therapy data.

9.1.2 Pre-Treatment Screening Phase (Day -28 to -1)

The Screening Phase may last up to 28 days prior to the first administration of study drug. Procedures outlined in the Schedule of Assessments (Section 8.1.3) will be conducted during this time and will include the following activities and procedures:

- Assess eligibility (according to the inclusion and exclusion criteria).
- Obtain informed consent.
- Collect pertinent medical history, including concomitant illnesses/diseases and concomitant medications (prescription medications, over-the-counter medicines and supplements, and alternative/herbal therapies).
- Collect cancer treatment history and update prior cancer therapy data as needed.
- Record vital signs.
- Perform a physical examination.
- Conduct a neurological examination based on the NANO criteria.
- Assess KPS.
- Perform an electrocardiogram (ECG).
- Perform echocardiogram or multigated acquisition scan (MUGA).
- Collect samples for hematology (complete blood count [CBC]) and serum chemistry tests.
- Collect samples for urinalysis (24-hour urine protein as needed).
- Assess coagulation parameters.
- Conduct pregnancy test in women of childbearing potential.
- Collect samples for serology tests for HIV antibody, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C virus antibody tests.

- Perform DWI-MRI, conventional MRI, and mRANO assessment of response.
- Archival tumor tissue sample must be collected for WT1 by IHC and CISH where available. Provision of tissue samples is preferred but not mandatory to be eligible for the study. WT1 IHC and CISH will be performed even if the data expression of WT1 are available from medical records.
- Tumor tissue samples will be requested for retrospective biomarker analysis; however, this is optional and requires additional consent from the patient.
- Assess isocitrate dehydrogenase (IDH) 1 and 2 mutations and MGMT promoter methylation status. It is strongly encouraged for sites to provide archival tumor tissue (if available) if no information regarding IDH 1 and 2 mutation and MGMT promotor methylation status is available at enrollment.
- Collect blood for CTL induction analysis (prior to drug administration).
- Collect blood for retrospective analysis of biomarkers (prior to drug administration). Additional consent is needed prior to collection of blood samples for these biomarkers.
- Pulse oximetry to measure O_2 saturation (SpO_2)
- Report AEs and SAEs.
- Patients should also be asked at this time for consent to provision of a sample of tumor tissue after the last dose of study medication, if the patient will be undergoing a medically necessary procedure (this is not mandatory). Patients can elect to participate or not participate in providing the optional tumor tissue throughout the study.

Patients who fail the Screening Phase may be re-screened at a later date. Rescreening for patients in Part 2 will be permitted for patients with laboratory values (AST, ALT, bilirubin, creatinine) that were out of range to meet eligibility, and for patients requiring dexamethasone doses in excess of 4 mg/day (or equivalent) once the dose can be tapered to 4 mg/day (or equivalent) or less with stability in the judgement of the investigator.

9.1.3 Induction Phase (Day 1, Day 8, Day 15, Day 22, and Day 29)

In Part 1, all patients will be dosed with DSP-7888 Dosing Emulsion every 7 ± 1 day and with Bev every 14 ± 3 days during the Induction Phase of the study.

In Part 2, patients randomized to the DSP7888 Dosing Emulsion plus Bev treatment group will be dosed with DSP7888 Dosing Emulsion every 7 ± 1 day during the

Induction Phase of the study. All patients will be dosed with Bev every 14 ± 3 days during the Induction Phase.

9.1.3.1 Day 1, Day 15, and Day 29 Procedures

The following procedures will be performed for all patients on Day 1, Day 15, and Day 29 of the Induction Phase:

- Record vital signs.
- Assess KPS.
- Collect samples for hematology (CBC) and serum chemistry tests.
- Collect samples for urinalysis (24-hour urine protein as needed).
- Administer DSP-7888 Dosing Emulsion plus Bev or administer Bev alone.
- Report AEs and SAEs.
- Record concomitant medications.
- Conduct a physical examination (Day 29 only).
- Conduct a neurological examination by NANO Criteria (Day 29 only).
- Collect blood for CTL induction analysis (prior to drug administration). (If blood is collected during Pre-Treatment Screening Phase, blood collection at Day 1 is not needed).
- Collect blood for retrospective analysis of biomarkers from the patients who have provided consent at Screening (prior to drug administration). (If blood is collected during the Pre-Treatment Screening Phase, blood collection at Day 1 is not needed).

9.1.3.2 Day 8 and Day 22 Procedures

Patients in the DSP-7888 Dosing Emulsion plus Bev treatment group will undergo the following assessments:

- Record vital signs.
- Assess KPS.

- Collect blood for additional HLA haplotypes (Day 8, or next cycle visit) prior to drug administration.
- Administer DSP-7888 Dosing Emulsion.
- Report AEs and SAEs.
- Record concomitant medications.

9.1.4 Consolidation Phase (Days 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, and 183)

All patients will be dosed every 14 ± 3 days during the Consolidation Phase of the study. The exception to this is the following:

- DSP-7888 Dosing Emulsion will not be administered at Day 183.

9.1.4.1 Days 43, 71, 99, 127, and 155 Procedures

- Record vital signs.
- Assess KPS.
- Collect samples for urinalysis (24-hour urine protein as needed).
- Administer DSP-7888 Dosing Emulsion plus Bev or administer Bev.
- Report AEs and SAEs.
- Record concomitant medications.

9.1.4.2 Days 57, 85, 113, 141, and 169 Procedures

- Conduct a physical examination.
- Conduct a neurological examination by NANO Criteria.
- Record vital signs.
- Assess KPS.
- Perform an ECG.
- Collect samples for hematology (CBC) and serum chemistry tests.
- Collect samples for urinalysis (24-hour urine protein as needed).

- Collect blood for CTL induction analysis (prior to drug administration) (Days 57, 85, 113, and 169 only).
- Collect blood for retrospective analysis of biomarkers from the patients who have provided consent at Screening (prior to drug administration) (Days 57, 85, 113, and 169 only).
- Administer DSP-7888 Dosing Emulsion plus Bev or administer Bev.
- Report AEs and SAEs.
- Record concomitant medications.
- Perform DWI-MRI, conventional MRI, and mRANO assessment of response (Days 57, 113, and 169 only).

9.1.4.3 Day 183 Procedures

- Record vital signs.
- Assess KPS.
- Report AEs and SAEs.
- Record concomitant medications.
- Administer Bev.

9.1.5 Maintenance Phase (Day 197 and Thereafter)

Patients in the DSP-7888 Dosing Emulsion plus Bev treatment group will be dosed with DSP-7888 Dosing Emulsion every 28 days ± 7 days and with Bev every 14 days ± 3 days during the Maintenance Phase of the study. Patients in the Bev alone treatment group will be dosed with Bev every 14 days ± 3 days during the Maintenance Phase.

The following assessments will be conducted:

- Conduct a physical examination (Day 197 and then every 4 weeks).
- Conduct a neurological examination by NANO Criteria (Day 197 and then every 4 weeks).
- Record vital signs.

- Assess KPS (Day 197 and then every 4 weeks).
- Collect samples for hematology (CBC) and serum chemistry tests (Day 197 and then every 4 weeks).
- Collect samples for urinalysis (24-hour urine protein as needed) (Day 197 and then every 4 weeks).
- Collect blood for CTL induction analysis (prior to drug administration) (Day 253 and then every 12 weeks thereafter).
- Collect blood for retrospective analysis of biomarkers from the patients who have provided consent at Screening (prior to drug administration) (Day 253 and then every 12 weeks thereafter).
- For patients in the DSP-7888 Dosing Emulsion plus Bev treatment group, administer DSP-7888 Dosing Emulsion every 28 days ± 7 days, and administer Bev every 14 days ± 3 days. For patients in the Bev alone treatment group, administer Bev every 14 days ± 3 days.
- Report AEs and SAEs.
- Record concomitant medications.
- Perform DWI-MRI, conventional MRI, and mRANO assessment of response (Day 253 and then every 12 weeks thereafter).

9.1.6 End of Treatment Visit

The reasons for the discontinuation of study treatment are described in Section 8.2.4. The following procedures should be conducted within 28 days after the last dose of study treatment (and prior to the initiation of any new post-study treatment):

- Conduct a physical examination.
- Conduct a neurological examination by NANO Criteria.
- Record vital signs.
- Assess KPS.
- Perform an ECG.
- Collect samples for hematology (CBC) and serum chemistry tests.

- Collect samples for urinalysis (24-hour urine protein as needed).
- Collect blood for CTL induction analysis (prior to drug administration).
- Collect blood for retrospective analysis of biomarkers from the patients who have provided consent at Screening (prior to drug administration).
- Perform DWI-MRI, conventional MRI and mRANO assessment of response.
- Report AEs and SAEs.
- Record concomitant medications.
- Tumor samples for WT1 by IHC and CISH and for retrospective analysis of biomarkers should be obtained from all patients who provide consent (per the point above). Provision of tumor tissue samples after the last dose of study drug is optional and not mandatory.

9.1.7 Follow-Up after End of Treatment

As the primary endpoint is OS, it is critical to follow patients for survival accordingly to the schedule.

The following survival follow-up methods are recommended:

- Direct (ie, telephone call or email to the patient/patient's relative, etc.), or
- Indirect (ie, medical record review or obituary listing review, etc.).

Patients who discontinue treatment for PD, and who are treated with alternative therapy will be followed for survival.

- The following procedures will be performed: Survival follow-up (direct or indirect methods as specified above) and post-treatment anti-tumoral therapy every 3 months and/or on an ad-hoc basis for safety or regulatory purposes, or a prespecified analysis.
- Follow-up of a patient for up to 90 days to ensure no pregnancy occurs in female patients of childbearing potential and in female partners of male patients.

Patients who discontinue treatment for PD (and who will not receive further treatment), or due to the need for a prohibited treatment for a concomitant illness or AE, an AE that precludes further administration of DSP-7888 Dosing Emulsion or Bev, the patient withdraws consent for continued administration of DSP-7888 Dosing Emulsion or Bev,

the Investigator believes it is in the patient's best interest to discontinue protocol therapy will undergo the following procedures:

- Survival follow-up (direct or indirect methods as specified above) and post-treatment anti-tumoral therapy every 3 months and/or on an ad-hoc basis for safety or regulatory purposes, or a prespecified analysis.

- Assess KPS and conduct a neurological examination by NANO Criteria on Day 57 ± 14 days, Day 113 ± 14 days and Day 169 ± 14 days if withdrawal of study treatment occurs prior to these time points and until the patient receives further treatment for GBM.

- Perform DWI-MRI, conventional MRI, and mRANO assessment of response on Day 57 ± 14 days, Day 113 ± 14 days and Day 169 ± 14 days if withdrawal of study treatment occurs prior to these time points and until the patient receives further treatment for GBM.

- Follow-up of a patient for up to 90 days to ensure no pregnancy occurs in female patients of childbearing potential and in female partners of male patients.

If a patient wishes to withdraw their consent to both study drug and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If the patient wishes to withdraw their consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the patient's notes and in the clinical study database.

The status of ongoing, withdrawn (from the study), and "lost to follow-up" patients at the time of an OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's current physician, and checking publicly available death registries. If the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Withdrawn patients will not be replaced.

For patients who are lost to follow-up; who move out of the Investigator's catchment area or are unable to continue to come to the investigational site; or in the event the Sponsor deems it necessary to discontinue the study, patients will be censored on the day the patient was last known to be alive or had not progressed.

9.2 Description of Study Procedures

9.2.1 Medical History

The medical history will include all pertinent aspects of the patient's past health, as well as aspects of the underlying GBM, including date of diagnosis, extent of surgery, MGMT promoter methylation and IDH-1 and -2 mutation, dose of RT administered, duration of chemotherapy, and date of recurrence or progression. All concurrent medications including prescription medications, over-the-counter medicines and supplements, and alternative/herbal therapies will be recorded. The medical history will be obtained during Screening.

9.2.2 Karnofsky Performance Status Score

Careful questioning, including time in bed or in a chair, ability to perform activities of daily living, degree of ambulatory ability, etc., will be assessed with the KPS.

9.2.3 Clinical Laboratory Evaluation

The hematology and clinical chemistry laboratory analyses will be performed at a central laboratory. Reference ranges will be supplied and used by the Investigator to assess the laboratory data for clinical significance and pathological changes. While the expectation is that samples will be analyzed by a central laboratory, local laboratories may be used as deemed necessary by the Investigator in order to make treatment related decisions. Note that eligibility will always be determined from the central laboratory results. If a sample is analyzed by a local laboratory, an aliquot will be also be sent to the central laboratory as required by this protocol.

9.2.3.1 Hematology

A CBC will include measures of the white blood cell count (WBC), red blood cell count, hemoglobin, hematocrit, WBC (total and differential), and platelet count. A CBC will be performed according to the Schedule of Assessments in Section 8.1.3.

9.2.3.2 Coagulation Parameters

Coagulation parameters will include an INR and PTT. Coagulation parameters will be obtained during Screening and then as clinically indicated.

9.2.3.3 Clinical Chemistry

Serum chemistry tests will include measures of creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, sodium, potassium, chloride, bicarbonate, glucose, uric acid, calcium, magnesium, and phosphorus. Serum chemistries will be performed according to the Schedule of Assessments in Section 8.1.3.

9.2.3.4 Urinalysis

A urinalysis will include measurements of pH, specific gravity, and dipstick determinations of protein, glucose, ketones, blood (or hemoglobin) and total bilirubin. If any dipstick determinations are 2+ or greater, a microscopic examination of urine will be performed. If a dipstick determination of protein is 2+ or higher, a 24-hour urine collection must be done. Urine testing will be performed according to the Schedule of Assessments in Section 8.1.3.

9.2.3.5 Other Laboratory Variables

Screening for hepatitis B surface antigen, hepatitis C antibody, HIV will be performed at Screening/Baseline only.

Pregnancy testing in women of childbearing potential may be obtained with a serum or urine beta human chorionic gonadotropin test. A pregnancy test will be performed during Screening and then as clinically indicated.

9.2.4 Vital Signs

Vital signs will include systolic and diastolic blood pressures, pulse, respiratory rate, temperature, and weight. Blood pressure and heart rate will be recorded in a standardized manner, ie, after the patient has rested in the sitting position for at least 5 minutes. Pulse oximetry will also be measured at screening only.

9.2.5 Physical Examination

A physical examination will include examinations of the skin, particularly areas where DSP-7888 Dosing Emulsion has been administered; head, eyes, ears, nose, and throat; chest, including the lungs and the heart; abdomen; and extremities and areas of major lymph node chains.

9.2.6 Neurological Examination

A neurological exam will be based on the NANO criteria (Appendix 16.3) and will include assessments of gait, strength, ataxia, sensation, facial strength, visual fields, language, and level of consciousness.

9.2.7 Tumor and Brain Imaging

Conventional MRI and DWI scans will be obtained at Screening; at Weeks 8, 16, and 24 of the study; and then every 12 weeks thereafter; and at EOT or as clinically indicated. A radiology manual will describe in detail the techniques for obtaining, storing, transmitting, and interpreting the images (including mRANO evaluation). Clinical decisions (including mRANO assessments) will be made based on local interpretation of the MRIs. In cases of suspected progression, confirmatory MRIs are to

be performed 4-8 weeks later (see Appendix 16.2). Continuation of study treatment is independent from the radiological assessments.

9.2.8 Other Safety Assessments

9.2.8.1 Electrocardiogram

A 12-lead ECG will be obtained during Screening, days 57, 85, 113, 141, 169, and EOT.

9.2.8.2 Echocardiogram/MUGA

An echocardiogram or MUGA will be conducted during Screening.

9.2.8.3 Monitoring of QTc Intervals

Rationale for Use of QTcF

Per the FDA's Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, "Bazett's correction is frequently used in clinical practice and in the medical literature. In general, however Bazett's correction overcorrects at elevated heart rates and undercorrects at heart rates below 60 beats per minute and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's in subjects with such altered heart rates.

Recommendations for the Management of Prolonged QTc Intervals and Electrolyte Imbalances

Patients who experience prolongation of the QTc interval to > 480 msec (CTCAE Grade 2) should be promptly evaluated for causality of the QTc prolongation and managed according to the following guidelines:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range. Patients with CTCAE ≥ 2 with hypomagnesemia (magnesium < 0.5 mmol/L) and/or hypokalemia (potassium < LLN - 3.0 mmol/L) should receive electrolyte supplementation.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.

9.2.9 Pharmacodynamic Testing

Peripheral blood mononuclear cells will be obtained for the evaluation of WT1 peptide-specific CTL induction activity by tetramer assay. Furthermore, if consent is given, analysis will be conducted of other biomarkers from tumor tissue and peripheral

blood samples, such as protein and gene expression analysis that may be important to the understanding of DSP-7888 Dosing Emulsion, but that have not yet been determined. Providing informed consent for use of this sample for these research purposes is optional, and participation in the study is not dependent upon providing this sample.

Immunohistochemistry of FFPE tumor tissue will be performed to evaluate expression of WT1 by IHC and CISH, even if those expression data are available from medical records. FFPE slides will be requested.

Site study staff will ship tissue samples to the central laboratory. Remaining tissue slides will be returned to the sites at the conclusion of testing or at a time requested by the study site.

Specific shipping and processing instructions will be detailed in the study Laboratory Manual.

9.3 Duration of Treatment

Patients will continue to receive DSP-7888 Dosing Emulsion plus Bev or Bev alone: independent of radiological assessment / progression:

1. Provided that the Investigator considers it to be safe for the patient
2. Provided that the Investigator determines that there is potential benefit for the patient
3. When the patient is willing to continue

10 EFFICACY, PHARMACODYNAMICS, AND SAFETY VARIABLES ASSESSED

The planned schedule of assessments is available in Section 8.1.3.

10.1 Efficacy Variables

The primary efficacy variable will be the comparison of OS between treatment with DSP-7888 Dosing Emulsion plus Bev versus Bev alone in patients with recurrent or progressive GBM following initial therapy.

The key secondary efficacy variable is the 12-month survival rate between treatment with DSP-7888 Dosing Emulsion plus Bev versus Bev alone. The other secondary efficacy variables include:

- PFS of DSP-7888 Dosing Emulsion plus Bev versus Bev alone
- Six-month PFS of DSP-7888 Dosing Emulsion plus Bev versus Bev alone
- Response rate of DSP-7888 Dosing Emulsion plus Bev versus Bev alone
- Duration of response of DSP-7888 Dosing Emulsion plus Bev versus Bev alone

10.2 Pharmacodynamic Assessments

Pharmacodynamic assessments will include:

- The evaluation of WT1 peptide-specific CTL induction activity
- Immunohistochemistry and CISH to evaluate expression of WT1.

10.3 Safety Assessments

Safety will be evaluated based on the AEs recorded at each contact with the patient, physical examinations, and the results of laboratory tests; the severity of AEs or abnormal laboratory results will be based on the CTCAE V4.03.

10.3.1 COVID-19

Because much is still unknown about how SARs-CoV-2 affects the human body, patients who have tested positive for COVID-19 will be identified and relevant information collected. All patients should provide documentation of any testing for COVID-19 if available, along with test results, both at screening for enrollment and/or during the study. Prior test results should be reported, if available, for any patient who has previously tested positive for COVID-19 SARS-CoV-2 titers (antiviral immunoglobulin G [IgG] and immunoglobulin M [IgM]).[38] These data will be entered into the patient's study-specific record.

Any patient-reported illness of COVID-19 during the study should be recorded as an AE. If a patient reports infection with COVID-19, the investigator may discuss with the Medical Monitor whether the patient can continue on study.

10.3.2 Adverse Events

10.3.2.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the

medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, inter-current illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs. Disease progression and lack of efficacy are not considered to be an AE or SAE, and the duration of AE collection is until 30 days after the last dose of study drug.

It is the responsibility of the Investigator to document all AEs that occur during the study from the time main consent is obtained until 30 days after the last dose of study drug. When an SAE that is assessed as causally related (ie, Definite, Probable, or Possible) occurs after completion of the clinical study, the Investigator will report the event to the Sponsor as a spontaneous report. Adverse events will be elicited by asking the subject a non-leading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” Adverse events should be reported on the appropriate page of the eCRF.

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study patient represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgement) should not be recorded as AEs; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered AEs.

Adverse reactions will be reported to the FDA according to 21 Code of Federal Regulations (CFR) 312.32.

10.3.2.2 Assessment of Severity

The severity of AEs or abnormal laboratory results will be based on the CTCAE V4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Each AE will be assigned a category by the Investigator as follows:

Grade 1: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities

Grade 2: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed

Grade 3: An AE that prevents normal everyday activities; treatment or other intervention is usually needed

Grade 4: An AE that places the subject at immediate risk of death as the event occurred

Grade 5: An AE that results in the death of the subject

If there is a change in the severity of an AE, it must be recorded as a separate event.

10.3.2.3 Assessment of Causality

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Inherent in this definition is the need for the Investigator and Sponsor to evaluate the available evidence and make a judgement about the likelihood that the drug actually caused the AE.

Every effort will be made by the Investigator to assess the relationship of the AE, if any, to either or both of the drugs (i.e., DSP-7888 Dosing Emulsion and Bev) comprising protocol therapy. Causality should be assessed using the following categories:

Not Related to the Study Drug:

Not Related: Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.

Unlikely: Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.

Related to the Study Drug:

Possible: Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.

Probable: Clinical event with a reasonable time relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Definite: Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

10.3.2.4 Action Taken

The Investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

10.3.2.5 Follow-Up of Adverse Events

All Investigators should follow up patients with AEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

10.3.2.6 Documentation and Reporting of Adverse Events

All AEs, whether serious or not, will be described in the source documents and the AE page of the eCRF. A medical condition present at Screening that has increased in frequency or severity during the AE reporting period must also be recorded as an AE.

Patients should be instructed to report any AE that they experience to the Investigator. Investigators should assess the patient for AEs at each visit. AEs occurring during the clinical study and the follow-up period should be recorded on the appropriate AE page of the eCRF. To capture the most potentially relevant safety information during a clinical study, it is important that Investigators use accurate AE terminology on eCRFs.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF.

Appropriate CTCAE terms for AEs should be used whenever possible. If an appropriate CTCAE term is not available, then the verbatim term should be documented.

The symptoms that occur with injection site reaction should be reported as "injection site reaction" (not described as "erythema," "itching," etc.).

Information to be reported in the description of each AE must include at a minimum:

- The patient's study number
- A medical diagnosis
- Date of onset
- Date of resolution
- The severity of the event
- Whether the event is serious
- Action taken regarding study drug (none, dose reduction, temporary interruption, discontinuation)
- The outcome of the event (patient recovered without sequelae, patient recovered with sequelae, event is ongoing, patient expired)
- The relationship of the event to study drug

Questions sometimes arise about when an abnormal laboratory value should be reported as an AE. Although this decision is at the discretion of the Investigator, an abnormal laboratory value should be reported as an AE if it is clinically significant; if it is associated with clinical sequelae; if it is an SAE or important medical event; if it requires a discontinuation or change in protocol therapy; if it requires medical intervention; or if it results in study discontinuation.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE. It is more advantageous to report a laboratory abnormality as a clinical event with a medical term rather than an abnormal laboratory result per se (record thrombocytopenia rather than decreased platelet count).

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE.

The Investigator is responsible for ensuring that all AEs (as defined in Section 10.3.2 and as further specified below) observed by the Investigator or reported by patients are collected and recorded in the patients' medical records in the eCRF, and for SAEs, on the SAE report form. These AEs will include the following:

- All non-serious AEs (as defined in Section 10.3.2.6) that occur after the patient has signed the main informed consent form (ICF) until 30 days after the last dose of study drug.

- All SAEs (as defined in Section 10.3.3.1) that occur after the patient has signed the main ICF until 30 days after the last dose of study drug.

The following AE attributes must be assigned by the Investigator: AE diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to the investigational product or active control, and action taken. The Investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRFs.

- Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event

- Classification of "serious" or "not serious"

- Severity

- Date of first occurrence and date of resolution (if applicable)

- Action taken

- Causal relationship to DSP-7888 Dosing Emulsion alone

- Causal relationship to Bev alone

- Outcome of the event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

Patients should be advised to immediately alert the study staff if they experience AEs that could be new or worsening signs or symptoms of an acute cardiac and/or respiratory event:

- Chest tightness/pain

- Coughing or dyspnea

- Wheezing

- Fatigue

10.3.2.6.1 Reporting COVID-19 Infections

Suspected or confirmed COVID-19 infections, including asymptomatic infections and positive COVID-19 tests, are Adverse Events of Special Interest (AESIs), and therefore immediately reportable events, even if the events do not meet SAE criteria.

Serious COVID-19 events will be reported on an SAE Report Form within 24 hours of the Investigator's awareness, according to Section 10.3.3.1.1.

Non-serious COVID-19 events will be reported on a COVID-19 Report Form within 5 calendar days of the Investigator's awareness to the same email / fax for reporting SAEs described in Section 10.3.3.1.1.

Updates or follow-up information for COVID-19 events should be reported on an SAE Report Form (serious events) or a COVID-19 Report Form (non-serious events) within the same timelines as initial reports.

10.3.3 Serious Adverse Events

10.3.3.1 Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose:

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing, non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination pages of the eCRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any

event that the Investigator regards as serious that did not strictly meet the criteria above, but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Hospitalizations for elective or planned purposes, for the administration of protocol therapy, for the administration of blood products or ancillary therapies, for procedures such as endoscopy or placement of an intravascular access device, for purposes of disposition or respite care or that are less than 24 hours in duration would not fulfill the above definition of serious. Complications arising from elective or planned hospitalizations that result in prolonged hospitalization would be considered SAEs.

10.3.3.1.1 Reporting of Serious Adverse Events

Any SAE must be reported by the Investigator if it occurs from the time the patient signs the main ICF until 30 days after the last dose of study drug, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, which includes the concomitant medication information. A copy of these forms must be emailed **within 24 hours** to the attention of the Sponsor at:

SDP Oncology Pharmacovigilance Department
Email: BBISafety@bostonbiomedical.com
Fax (back-up to email): (617) 674-8660

The Investigator should not wait to receive additional information to document fully the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety if brought to the attention of the Investigator at any time after the cessation of study drug administration and linked by the Investigator to this study, should be reported to the study monitor.

The Sponsor and/or INC Research (A Syneos Health Group Company) will promptly notify all relevant Investigators and the regulatory authorities of findings that could adversely affect the safety of patients, have an impact on the conduct of the study, or alter the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval/favorable opinion of the study. In addition, INC Research (A Syneos Health Group Company), on behalf of the Sponsor, will expedite the reporting to all concerned Investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Patients will be instructed that a known or suspected pregnancy occurring during the study, in patients or the female partners of male patients, should be confirmed and reported to the Investigator, who will then withdraw the patient from the study without delay. Upon discontinuation from the study, only those procedures that would not expose the patient to undue risk will be performed. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term; and the status of mother and child will be reported to the Sponsor after delivery.

10.3.3.1.2 Unexpected Adverse Reactions

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (Investigator's Brochure for DSP-7888 Dosing Emulsion or local product information for Bev).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The Sponsor and/or INC Research (A Syneos Health Group Company) shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the Sponsor of such a case. All Investigators should follow up SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Suspected unexpected serious adverse reactions that occur after the patient has withdrawn from the clinical study must be reported by the Investigator to the Sponsor.

10.4 Pharmacodynamic Variables

The relationship between pharmacodynamic parameters such as WT1 peptide-specific CTL activity and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion will be described if appropriate.

The relationship between expression of WT1 by IHC and CISH in tumor tissue and certain clinical findings (eg, OS, response) in patients receiving DSP-7888 Dosing Emulsion will be described if appropriate.

10.5 Independent Data Monitoring Committee

To enhance the safety and integrity of the study data, an IDMC consisting of independent experts will be convened to periodically review the accumulating safety data and efficacy results of the interim analyses. The specific responsibilities and

composition of the IDMC will be outlined in a separate document, the IDMC Charter. The charter will specify when the IDMC will convene to review accumulating safety data and to provide a recommendation on study continuation or early termination in case there is a concern regarding safety. Results of the interim analyses of primary efficacy and other available data, including safety data, will be reviewed by the IDMC. More details for decision making based on the results of the IAs will be provided in the IDMC Charter.

10.5.1 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

11 STATISTICAL ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

11.1 Statistical Methods

The primary data from Part 1 of the study will be listed and summarized separately from the data from the randomized part of the study. Only descriptive statistics will be used to present data from Part 1 of the study. Summaries will be provided for each dose level.

The methodology for the randomized Part 2 of the study is presented in the sections below.

11.1.1 Statistical Hypotheses

The primary statistical null hypothesis is that there is no difference between the 2 treatment groups (DSP-7888 Dosing Emulsion plus Bev and Bev alone) with regards to OS. This will be tested by a stratified log-rank test.

The statistical null hypothesis for the key secondary endpoint is that there is no difference between the 2 treatment groups (DSP-7888 Dosing Emulsion plus Bev and Bev alone) with regards to 12-month OS rate. Treatment comparisons will be performed using the respective KM estimates and the respective variances according to the Greenwood's formula to construct a standard normally distributed Z-statistic.[39]

11.1.2 Level of Significance, Multiple Comparisons, and Multiplicity

Primary efficacy and the key secondary endpoint will be tested using a 1-sided test with an overall significance level 2.5%. The Lan-DeMets error spending function based on O'Brien-Fleming stopping boundaries will be used to adjust the significance level for the interim and the final analysis. The key secondary endpoint will only be tested following the significance of the primary endpoint. The details of multiplicity adjustment for the adaptive design will be provided in the SAP.

11.2 Definition of Study Populations

The ITT population will consist of all randomized patients in Part 2 of the study, regardless of whether treatment is ever administered. The primary efficacy endpoint of OS will be analyzed based on the ITT population.

The per protocol (PP) population will consist of all patients in the second part of the study who are eligible for enrollment into the study who receive at least one dose of study drug (DSP-7888 Dosing Emulsion or Bev), and who do not have major protocol deviations that may impact primary analysis of efficacy. The determination of the PP population will be finalized following a complete data review by both INC Research (A Syneos Health Group Company) and Sponsor representatives prior to the database lock.

The safety population will consist of all patients who receive at least one dose of study drug (either DSP-7888 Dosing Emulsion or Bev).

The DLT population will consist of all patients in Part 1 of the study who receive the first 5 administrations of the combination of DSP-7888 Dosing Emulsion plus Bev or who are discontinued from the study during this time due to the occurrence of a DLT and who do not have major protocol deviations that may impact primary analysis of efficacy.

11.2.1 Determination of Number of Events, Power and Sample Size

Considering that the number of death events are 108 (observed at IA1), approximately 185 (IA2), and approximately 260 (FA), the study will have approximately 90% power to detect a 34% reduction in the HR of DSP-7888 Dosing Emulsion plus Bev versus Bev alone (ie, HR = 0.663, which corresponds to a 1-year survival proportion of 45% in the DSP-7888 Dosing Emulsion plus Bev arm compared to 30% in the Bev alone arm). The number of death events at the FA could go up to 370 if event re-estimation is performed based on the conditional power calculated at IA2. Assuming an enrollment rate of 11 patients per month and patients are followed until the end of the study, with a 5% dropout rate per year, the study is expected to enroll approximately 338-480 patients.

Note that Part 2 is an event-driven adaptive trial and statistical power of Part 2 is determined by the target number of death events instead of the number of patients. The actual number of randomized patients in Part 2 may vary to observe the targeted number of events, depending on the outcome of the interim analyses, the duration of the study and operational feasibility. It is envisioned that approximately 215 patients will be enrolled at the second IA with 185 events, approximately 338 patients will be enrolled at the FA with 260 events when there is no event number re-estimation. If the number of events at the FA reaches the cap of 370 with event number re-estimation, approximately 480 patients will be enrolled in the study assuming that the ratio of the number of events to the number of patients at the FA is approximately 0.77 (assume similar death event rate of 260/338 when the target event number is 260).

11.3 Demographic and Other Baseline Characteristics

All demographic and baseline characteristics information will be summarized using the ITT population. Extent of surgical resection in primary therapy (GTR versus not GTR)

and KPS class (60 through 70 versus 80 through 100) will be used as the stratification factors at randomization, and therefore will be considered to be the main covariate in the analysis of efficacy. In addition, gender, and age groups (< 55, 55 through 64, 65 through 74, 75 through 84, ≥ 85), and IDH mutation and MGMT methylation status will be considered to be relevant.

11.4 Planned Analyses

All efficacy analyses will be based on the ITT population. Analyses will be repeated using the PP population.

For survival-type endpoints (OS, PFS, duration of response), descriptive summary statistics that are of interest, point estimates, and 95% CI intervals for overall and PFS probabilities will be provided for each treatment group at 3, 6, 9, 12, 15, 18, 21, and 24 months, if estimable. These estimates will be computed from KM survival curves.

11.4.1 Demographic and Other Baseline Characteristics

All demographic and baseline characteristics information will be summarized using the ITT population. Karnofsky Performance Status scores (classified as 60 through 70 versus 80 through 100) and extent of surgical resection in primary therapy (GTR versus not GTR) will be used as stratification factors at randomization, and therefore will be considered to be the main covariate in the analysis of efficacy. In addition, gender and age groups (< 55, 55 through 64, 65 through 74, 75 through 84, and ≥ 85) and IDH mutation and MGMT methylation status will be considered to be relevant.

11.4.2 Planned Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint is OS. The KM method will be used to estimate and visualize the distribution of OS by treatment group. Additionally, KM curves and estimates by treatment group will be provided for the subgroups of patients within each randomization stratum (KPS 60 through 70, KPS 80 through 100, and extent of surgical resection in primary therapy [GTR versus not GTR]). The primary treatment comparison will be based on a stratified logrank test considering the 2 randomization factors of KPS class and extent of surgical resection in primary therapy (GTR versus not GTR). A stratified Cox's regression model will be performed with treatment group as the independent variable and the 2 randomization variables of KPS class (60 through 70 versus 80 through 100) and extent of surgical resection in primary therapy (GTR versus not GTR) as strata. Hazard ratio and respective 95% CI obtained from the stratified Cox model will be provided.

For patients who discontinue early or who complete without meeting the event (= death), the OS will be censored on the last day they were known to be alive.

11.4.3 Planned Analysis for Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is 12-month survival rate which is defined as the proportion of patients alive 12 months after randomization. Treatment comparisons will be performed using the respective KM estimate and the respective variances according to the Greenwood's formula.[38]

11.4.4 Planned Analysis for Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

- PFS is defined as the interval between randomization and progression, determined by central radiology review, or death from any cause. Pseudo-progression will not be considered as PD for the assessment of PFS, but only confirmed PD cases. PFS will be analyzed similarly to OS.

- Six-month PFS rate is defined as the proportion of patients alive at 6 months after randomization and without progressive neoplastic disease. Six-month PFS will be estimated considering only progressions determined by central radiology review or death as events. Six-month PFS will be analyzed similarly to 12-month survival rate.

- The ORR is defined as the proportion of patients who achieve CR or PR based on the mRANO criteria as determined by central radiology review. The absolute and relative frequency of ORR (CR plus PR) will be presented by treatment group in overall and within each randomization stratum (KPS 60 through 70, KPS 80 through 100, and extent of surgical resection in primary therapy [GTR versus not GTR]) and will be compared by the Cochran-Mantel-Haenszel test accounting for randomization strata. The odds ratio and CI obtained from the Cochran-Mantel-Haenszel will be provided.

- The duration of response is defined as the interval between first documented oncological response and progression of disease or death from any cause, with response based on the mRANO criteria as determined by central radiology review. Pseudo-progression will not be considered as PD for the assessment of duration of response endpoints, but only confirmed PD cases. Duration of response will be analyzed similarly to OS.

- For the calculation of PFS and duration of response, progression determined by central radiology review of the MRI results will be used as events. Table 5 summarizes the calculation approach for PFS considering the various situations for censoring. This table follows the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007. Further details for the analysis of the PFS will be provided in the SAP.

Table 5: **Calculation of PFS-Based Results of Centralized Review**

Situation	Date of Progression or Censoring	Outcome
No baseline radiological assessments	Randomization	Censored
Confirmed PD (by central radiology review)	Date of radiological assessment showing PD	Event
No death or confirmed PD	Date of last adequate radiological assessment	Censored
Treatment discontinuation for clinical (unconfirmed) progression	Date of last adequate radiological assessment	Censored
Treatment discontinuation for toxicity or reason other than confirmed PD, clinical progression, or death	Date of last adequate radiological assessment	Censored
New anticancer treatment started with no confirmed PD beforehand	Date of last adequate radiological assessment before start of new treatment	Censored
Death during the study before confirmed PD	Date of death	Event
Treatment discontinuation for other than confirmed PD or death, and no post-baseline radiological assessments	Randomization	Censored

Note: An adequate radiological assessment is one that is evaluable according to mRANO criteria by review of MRI results.

11.4.5 Planned Analysis for Pharmacodynamic Endpoints

Pharmacodynamic assessments will include:

- The evaluation of WT1 peptide-specific CTL induction activity
- Immunohistochemistry to evaluate expression of WT1 by IHC and CISH

To analyze the frequencies of the WT1-specific CTLs by tetramer assay, immunological responses would be defined to be positive when the frequencies of WT1-specific CTLs determined by tetramer assay increased significantly at least at one time point after the WT1 vaccination compared to those of WT1-specific CTLs before the WT1 vaccination. Possible correlations between clinical efficacy (eg, OS, ORR) and immunological responses would be examined in patients with both clinical and immunological responses available for assessment. The results would be used to examine whether there is a significant correlation between increases in the frequencies of WT1 peptide-specific CTLs and clinical responses.

For patients with tumor samples, a determination of expression of WT1 in tumor tissue from patients with solid tumors will be done by IHC and CISH. These tumor tissue samples will be obtained before the first dose of study drug and after the last dose of study drug (optional). The pathological assessment based on the proportion (%) of the stained tumor cells and the staining intensity for WT1 of each patient will be reported. Possible correlations between clinical efficacy (eg, OS, ORR) and the pathological assessment would be examined in patients with both clinical and immunological responses available for assessment.

11.4.6 Safety Analyses

Safety analysis and other summaries based on the safety population will be presented by actual treatment received. Safety evaluation will include assessments of AEs, serum chemistry, hematology (CBC), urinalysis, coagulation parameters, pregnancy, neurological examination, KPS, study drug exposure, vital signs, physical examination, and ECG.

Analyses of the safety parameters will be presented by visits and/or time points where data are collected. For continuous variables, descriptive statistics will include the number of patients (n), mean, standard deviation, median, minimum, and maximum. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of patients with no missing data, ie, will add up to 100%. Categorical variables with a non-zero number of missing values will include an additional “Missing” category with no percentage provided (the category will be excluded from the distribution).

Patient incidence rates of all treatment-emergent AEs will be tabulated by system organ class and preferred term. Tables and/or narratives of “on-study” deaths and serious and significant treatment-emergent AEs, including early withdrawals due to AEs, also will be provided. The extent of study exposure defined as the ([last exposure date] - [first exposure date] + 1) would also be summarized descriptively.

11.4.7 Additional Analyses

Subgroup analyses will be presented for selected efficacy and safety outputs. Relevant subgroups include, but are not limited to, geographic region, race, gender, age group, baseline KPS score, and extent of surgical resection in primary therapy (GTR versus not GTR). Details of subgroup analyses as appropriate will be presented in the SAP.

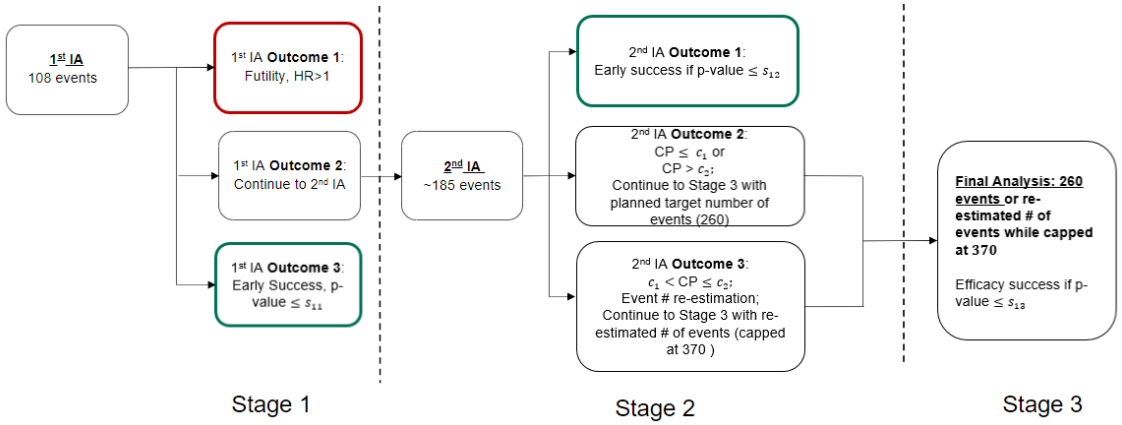
11.5 Periodic Safety Reviews

Interim safety data will be provided to the IDMC that will periodically convene to review accumulating safety data and to provide a recommendation on study continuation or early termination in case there is a concern regarding safety. The details of the data outputs that will be provided for the meetings will be referenced in the IDMC Charter.

11.6 Interim and Final Analyses

An adaptive design with 2 IAs and 1 FA is employed in Part 2 of this trial. Figure 3 presents the 3 stages of the adaptive design for Part 2 of the Study.

Figure 3: Adaptive Design for Part 2 of the Study



Abbreviations: CP = conditional power; HR = hazard ratio; IA = interim analysis.

Interim analysis 1 was carried out after 108 death events; IA2 will be carried out after approximately 185 death events and the FA will be carried out after approximately 260 death events or the target re-estimated number of death events occur. The target death event re-estimation will be determined by calculating the conditional power (CP) based on the IA2 results. The CP is defined as the probability of establishing a significant treatment effect on OS at the FA conditional upon the OS data available at IA2.

If the 1-sided p-value at IA1 is less than or equal to the prespecified significance levels$_{11}$, an early efficacy would be claimed. If the HR at IA1 is greater than 1, then the

study may be stopped for futility. The futility boundary is non-binding and the totality of data including other efficacy and safety data may weigh in the futility decision making besides the futility criteria for the HR.

Should the study neither stop for futility nor claim early efficacy at IA1, the study will continue to IA2. The IA2 decision rules are described as follows: if the 1-sided p-value at IA2 is less than or equal to the prespecified significance level s_{12}, an early efficacy will be claimed. In this case, the primary endpoint is reached by IA2, and the study may be concluded to be successful and the CSR may be written based on IA2.

If the early efficacy cannot be claimed at IA2, the event re-estimation will be performed using CP. This rule will be defined using 2 thresholds for CP, denoted by c_1 and c_2. These thresholds define the "underpowered zone" where it is most sensible to increase the number of OS events. The total number of events at the FA may be modified after IA2 as follows:

- If CP $\leq c_1$, retain the original number of events (ie, 260 events).
- If CP $> c_1$ and CP $\leq c_2$, increase the number of events to achieve CP of 90% or up to a pre-defined cap (ie, 370 events).
- If CP $> c_2$, retain the original number of events (ie, 260 events).

When the FA is conducted and the 1-sided p-value is less than or equal to the pre-specified significance level s_3, then efficacy success in terms of the primary endpoint of OS will be claimed at the end of the study.

Details of the adaptive design and the interim and final analyses including the specifications for c_1, c_2, s_{11}, s_{12}, and s_{13} will be provided in the SAP.

11.7 Protocol Deviations

All deviations related to study inclusion or exclusion criteria, conduct of the study, patient management, or patient assessment will be identified and evaluated before database lock and will be described in the final clinical study report.

11.8 General Considerations

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the SAP and the clinical study report.

For continuous variables, descriptive statistics will include the number of patients (n), mean, standard deviation, median, minimum, and maximum. When needed, the use of other percentiles (eg, 10%, 25%, 75%, and 90%) will be mentioned in the relevant

section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of patients with no missing data, ie, will add up to 100%. Categorical variables with a non-zero number of missing values will include an additional "Missing" category with no percentage provided (the category will be excluded from the distribution). Fisher's exact test will be used for unstratified comparison of categorical variables.

Summaries based on the ITT and PP populations will be presented by planned treatment group, unless specifically stated otherwise. Safety analyses and other summaries based on the safety population will be presented by actual treatment received. All analyses will be performed using data pooled across sites. Patient listings of all data from the eCRFs as well as any derived variables will be presented.

All statistical comparisons will be made using 1-sided tests at the $\alpha = 0.025$ significance level unless specifically stated otherwise, and CI will be calculated at 95%, 2-sided.

All p-values will be rounded to 4 decimal places.

Percentage values will be printed with 1 digit to the right of the decimal point (eg, 52.3%, 8.9%). Dates will be printed as DDMMMYYYY. If only year and month are available, date will be displayed as MMMYYYY. If only year is available, then just YYYY will be displayed. Dates that are missing because they are not applicable for the patients are output as "NA," unless otherwise specified.

All analyses will be performed using data pooled across sites.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher.

Specifications for table, figures, and data listing formats can be found in the SAP specifications for this study.

All planned analyses will be conducted following a soft database lock. A hard database lock will occur prior to the final analysis.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.2 Monitoring

Data for each patient will be recorded on an eCRF. Data collection must be completed for each patient who signs an ICF.

In accordance with current Good Clinical Practice (cGCP) and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The Investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of the data contained within the eCRFs.

During the COVID-19 public health emergency, traditional on-site monitoring might be limited for reasons such as: (1) sites may not be able to accommodate monitoring visits (eg, due to staffing limitations or site closures); or, (2) monitors may not be able to travel to trial sites. When planned on-site monitoring visits are not possible, the reason should be documented and available for review by SDP Oncology and during FDA inspections.

12.3 Data Management and Coding

The Sponsor or INC Research (A Syneos Health Group Company) will be responsible for the activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the Data Management and Biostatistics Departments of INC Research (A Syneos Health Group Company).

Medical coding will use Medical Dictionary for Regulatory Activities for concomitant diseases and AEs and WHO Drug Dictionary for medications.

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

12.3.1 Data Collection/Electronic Data Capture

The Sponsor/INC Research (A Syneos Health Group Company) will provide eCRFs. The results from Screening including the pre-screening and data collected during the study (except clinical laboratory test results) will be recorded in the patient's eCRF. The Investigator will review and sign all eCRFs.

The study sites will use an electronic data capture (EDC) system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulations Part 11.

Password protected access to the EDC system will be enabled via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed eCRFs must be reviewed and electronically signed and dated by the Investigator.

The source documents for the data recorded in the eCRF may include:

- Outcome, severity, and seriousness of AEs
- Causality of an AE to the study drug
- Reason for concomitant medication use
- Reason for change in dose of the study drug
- Reason for patient's discontinuation

12.3.2 Records and Supplies

12.4 Drug Accountability

On receipt of the study drug, the Investigator (or designee) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The Investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The study monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the Investigator (or designee) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

12.5 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between INC Research (A Syneos Health Group Company) and the Sponsor.

12.6 Compensation

The patient will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the ICF.

13 ETHICS

13.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

13.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

13.3 Ethical Conduct of the Study

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, cGCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

13.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to cGCP.

If an informed consent cannot be obtained and documented from a prospective trial participant (or legally authorized representative) as a signed paper copy, the consent form may be provided electronically by the Investigator or designee.

Where a prospective trial participant (or legally authorized representative) is unable to print the informed consent document provided electronically by the Investigator or designee, an electronic signature process is not available, and the prospective trial participant must meet time-sensitive eligibility criteria, the Investigator may consider using the alternative process to satisfy FDA requirements for obtaining and documenting informed consent and IRB approval process (FDA Guidance on Conduct

of Clinical Trials of Medicinal Products during COVID-19 Public Health Emergency, July 2020).

The Investigator is responsible for ensuring that no patient undergoes any study-related examination or activity before that patient has given written informed consent to participate in the study.

The Investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The patient should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given ample time to consider the study. Patients will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A signed and dated copy of the patient's ICF will be provided to the patient or the patient's legally authorized representative.

It should be emphasized that the patient may refuse to enter the study or to withdraw from the study at any time, without consequences for further care or penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the patient's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study patients will be informed about this new information and re-consent will be obtained.

13.5 Patient Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study patient's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patient to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the patient's identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act, applicable to national and/or local laws and regulations on personal data protection.

14 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and the quality of the data produced. After completion of the study (end of study is defined as the date of the last visit of the last patient), all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of the clinical development of the investigational product. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). This material shall be forwarded to the Sponsor at the earliest feasible time, but not less than 45 days before submission of any publication or any public presentation. Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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16 APPENDICES

16.1 Performance Status Scores

16.2 The Modified Response Assessment in Neuro-Oncology (mRANO) Criteria

16.3 The Neurological Assessment in Neuro-Oncology (NANO) Criteria

16.4 Glucocorticoid Dose Equivalents

16.5 Table of Tissue Samples and Informed Consents Required

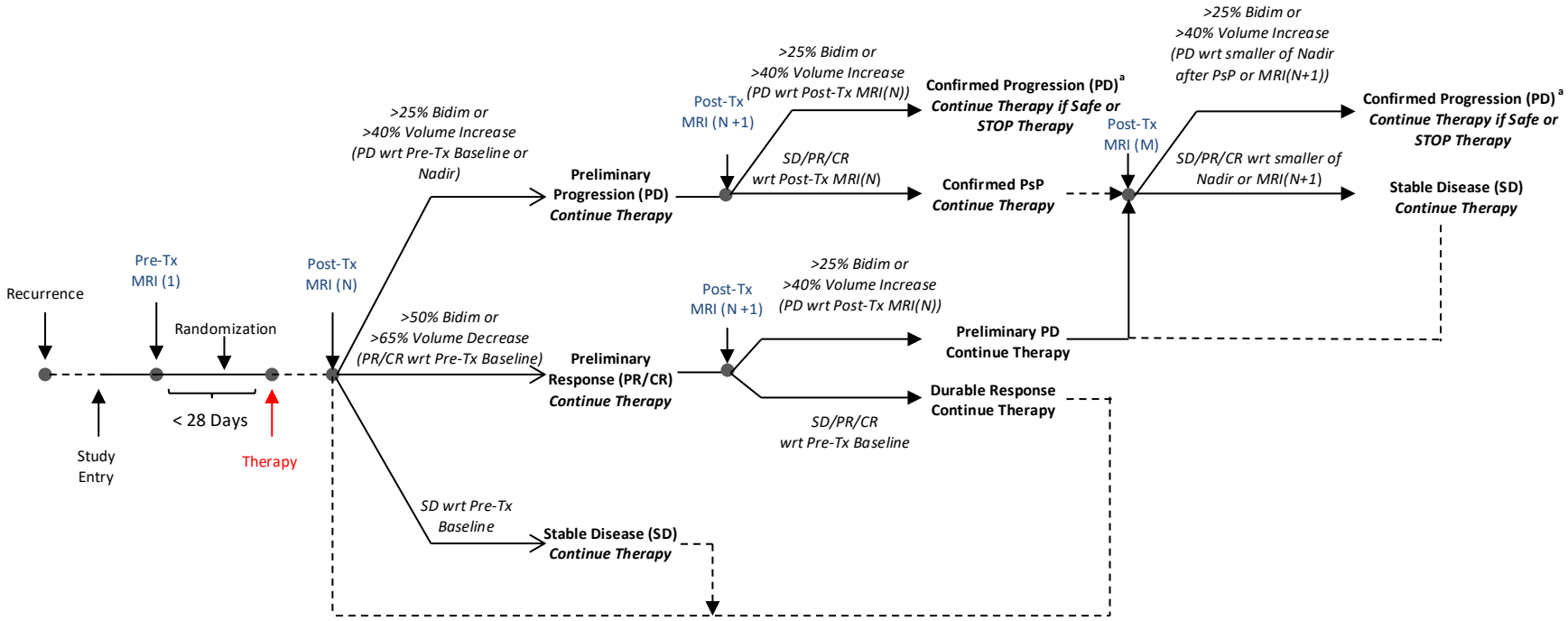
16.6 Investigator Signature Page

16.1 Performance Status Scores

ECOG Performance Status Scale		Karnofsky Performance Status Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	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.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

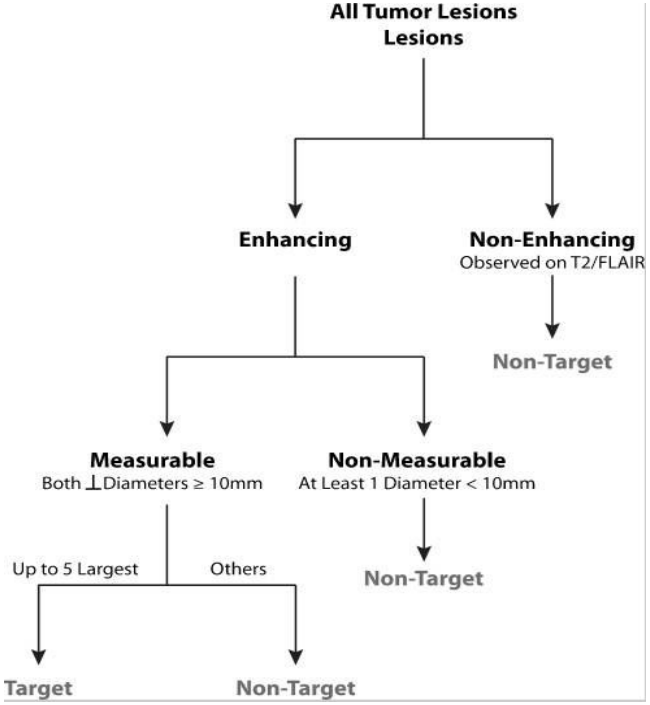
16.2 The Modified Response Assessment in Neuro-Oncology (mRANO) Criteria

Figure 4: Post-Randomization Tumor Assessment Process Flow



[a] Regular scan assessments (mRANO/NANO) should continue if patients do not receive any new treatment for their GBM.
To ensure harmonization across this multinational study, bidimensional measurements (rather than volume) were recommended.
The figure has been expanded from the original article: intext information has been added for clarification, based on communication with the lead author
(Ellingson BM, Wen, PY, Cloughesy, TF. Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials. Neurotherapeutics 2017;14:307-320).

Figure 5: Algorithm for Identification of Target Lesions



Note that both perpendicular measurements should be greater than or equal to 10 mm; otherwise, the lesion should be classified as non-target.

Measurable Lesions	**Non-Measurable Lesions**	**Target Lesions**
Contrast enhancing 2 perpendicular diameters both ≥ 10 mm* *If slice thickness plus interslice gap is >5 mm, minimum size for BOTH measurements should be 2 x slice thickness + 2 x interslice gap. e.g., slice thickness 5 mm, interslice gap 1.5 mm, minimum measurement = 13 mm.	Lesions too small to be measured (less than 10 mm in either of the perpendicular dimensions) Lesions that lack contrast enhancement (non-enhancing disease) Lesions with poorly defined margins that cannot be measured or segmented with confidence	Up to a total of 5 measurable lesions should be defined and ranked from largest to smallest

Lesion Assessments:

- Measure the sum of the products of the diameters of all target lesions
- Assess non-target lesions (all enhancing non-target lesions, non-enhancing disease)
- Look for new lesions (new measurable lesions should be added to the sum of bidimensional products)
- Combine lesion assessments with neurological/clinical findings and steroid use to yield an overall response

Complete Response (CR) Requires All of the Following:

Disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. The first scan exhibiting disappearance of all enhancing measurable and non-measurable disease is considered “preliminary CR”. If the second scan exhibits measurable enhancing disease with respect to the “preliminary CR” scan, then the response is not sustained, noted as pseudo-response and is now considered “preliminary PD” (note confirmed PD requires at least 2 sequential increases in tumor volume). If the second scan continues to exhibit disappearance of enhancing disease or emergence of non-measurable disease (less than 10mm bidimensional product), it is considered a

durable CR and the patient should continue on protocol therapy until reasons for discontinuing protocol therapy outlined in Section 8.2.4 are met..

Patients must be off corticosteroids (or on physiologic replacement doses only).

Stable or improved clinical assessments (i.e. neurological examinations).

Note: Patients with non-measurable disease only at baseline cannot have CR; the best response possible is SD.

Partial Response (PR) Requires All of the Following:

A decrease of ≥50% in sum of products of perpendicular diameters or ≥65% decrease in total volume of all measurable enhancing lesions compared with baseline, sustained for at least 4 weeks. The first scan exhibiting ≥50% decrease in sum of products of perpendicular diameters or ≥65% decrease in total volume of all measurable enhancing lesions compared with baseline is considered "preliminary PR". If the second scan exhibits PD with respect to the "preliminary PR" scan, then the response is not sustained, noted as pseudo-response and is now considered "preliminary PD" (note confirmed PD requires at least 2 sequential increases in tumor volume). If the second scan exhibits SD, PR, or CR, it is considered a durable PR and the patient should continue on protocol therapy until reasons for discontinuing therapy outlined in Section 8.2.4 are met.

Steroid dose should be the same or lower compared with baseline scan.

Stable or improved clinical assessments.

Note: Patients with non-measurable disease only at baseline cannot have PR; the best response possible is SD.

Progressive Disease (PD) is Defined by Any of the Following:

At least 2 sequential scans separated by ≥4 weeks both exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions. The first scan exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions should be compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response (on stable or increasing steroid dose) and is noted as "preliminary PD." If the second scan ≥4 weeks later exhibits a subsequent ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions relative to the "preliminary PD" scan, it is considered "confirmed PD" and the patient should discontinue protocol therapy. If the second scan ≥4 weeks later exhibits SD or PR/CR, this scan showing "preliminary PD" is noted as "pseudo-progression" and the patient should continue on protocol therapy until a second increase in tumor size relative to the

pseudo-progression scan is observed. Note that any new measurable (>10 mm × 10 mm) enhancing lesions should not be immediately considered PD, but instead should be added to the sum of bidimensional products or total volume representing the entire enhancing tumor burden.

In the case where the baseline or best response demonstrates no measurable enhancing disease (visible or not visible), then any new measurable (>10 mm x 10 mm) enhancing lesions are considered PD after confirmed by a subsequent scan ≥4 weeks exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions relative to the scan first illustrating new measurable disease. The first scan exhibiting new measurable disease is noted as "preliminary PD." If the second scan ≥4 weeks later exhibits a subsequent ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions relative to the "preliminary PD" scan, it is considered "confirmed PD," and the patient should discontinue protocol therapy if the definitions outlined in Section 8.2.4 are met. If the second scan ≥4 weeks later exhibits SD, CR, PR, or becomes non-measurable, this scan showing "preliminary PD" is noted as "pseudo-progression" and the patient should continue on protocol therapy until a second increase in tumor size relative to the "preliminary PD" or pseudo-progression, scan is observed. Note that any new measurable (>10 mm × 10 mm) enhancing lesions on the subsequent scan following the preliminary PD scan should not be immediately considered confirmed PD, but instead should be added to the sum of bidimensional products or total volume representing the entire enhancing tumor burden.

Clear clinical deterioration not attributable to other causes apart from tumor (eg, seizures, medication adverse effects, therapy complications, stroke, infection) or attributable to changes in steroid dose.

Failure to return for evaluation as a result of death or deteriorating condition.

Stable Disease (SD) Requires All of the Following:

Does not qualify for CR, PR, or PD as defined above. Note that this also applies to patients who demonstrate pseudo-response when the confirmation scan does not show PD or pseudo-progression when the confirmation scan does not show PR or CR.

In the event that corticosteroid dose was increased (for new symptoms/signs) without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that the steroid increase was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Overall Response Assessment:

Guidelines for determining comprehensive objective status

Target lesions (current scan)	Target lesions (previous scan)	New sites of measurable disease[a]	Neurological status	Steroid usage	Steroid dose	Overall objective status
CR	Not Evaluated	No	Stable/Better	No	N/A	Preliminary CR
PR	Not Evaluated	No	Stable/Better	Any	Stable/Decreasing	Preliminary PR
PD	Not Evaluated	Yes or No	Stable/Better	Any	Stable/Increasing	Preliminary PD
PD	Preliminary or Confirmed PR/CR	No	Stable/Better	Any	Stable/Increasing	Preliminary PD
SD	Preliminary or Confirmed CR/PR or SD/NE	No	Stable/Better	Any	N/A	SD
PR	Preliminary PR	Yes or No	Stable/Better	Any	Stable/Decreasing	Confirmed PR
SD	Preliminary PR	Yes or No	Stable/Better	Any	Stable/Decreasing	SD (Preliminary PR →Confirmed PR)
SD	Preliminary CR	Yes or No	Stable/Better	Any	Stable/Decreasing	SD (Preliminary CR →Confirmed CR)
CR	Preliminary CR	No	Stable/Better	No	N/A	Confirmed CR
SD	Preliminary PD	No	Stable/Better	Any	Stable/Decreasing	SD (Confirmed PsP)
CR/PR/SD PD/NE	CR/PR/SD/PD/NE	Yes or No	Worse	Any	Stable/Increasing	Confirmed PD
PD	Preliminary PD	Yes or No	Any	Yes	Stable/Increasing	Confirmed PD

[a]Note that new sites of measurable disease are added to the sum of bidimensional products or total lesion volume, or constitutes preliminary PD in the case of no measurable disease at baseline or best response

If there is uncertainty regarding whether there is progression, then PD confirmation is strongly encouraged by subsequent evaluations at 4-week intervals. If the subsequent evaluation confirms PD, then the date of progression should be the time point of the first assessment where PD was suspected.

16.3 The Neurological Assessment in Neuro-Oncology (NANO) Criteria

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Date Assessment Performed (day/month/year): _____

Study time point (ie, baseline, cycle 1, day 1) _____

Assessment performed by (please print name): _____

The Neurological Assessment in Neuro-Oncology (NANO) Criteria (continued)

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3 attempts
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

The Neurological Assessment in Neuro-Oncology (NANO) Criteria (continued)

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration

Definition of Neurologic Response:

An overall NANO score will be determined following assessment of each domain and will include one of 5 possible outcomes: neurologic response; neurologic progression; neurologic stability; not assessed; and non-evaluable.

NANO Category	Description
Neurologic Response	≥2-Level improvement in at least 1 domain without worsening in other domains from baseline or best level of function
Neurological Progression	1) ≥2-Level worsening from baseline or best level of function within ≥1 domain; or 2) Worsening to the highest score within ≥1 domain.
Neurological Stability	A score of neurologic function that does not meet criteria for neurologic response, neurologic progression, non-evaluable, or not assessed
Non-Evaluable	If it is more likely than not that a factor other than underlying tumor activity contributed to an observed change in neurologic function. Such factors may include changes in concurrent medications or a co-morbid event

In general, the assessment and scoring of all domains is encouraged.

16.4 Glucocorticoid Dose Equivalents

Equivalent Dose	Steroid
1.2 mg	Betamethasone (long-acting)
1.5 mg	Dexamethasone (long-acting)
8 mg	Methylprednisolone (intermediate-acting)
8 mg	Triamcinolone (intermediate-acting)
10 mg	Prednisone (intermediate-acting)
10 mg	Prednisolone (intermediate-acting)
40 mg	Hydrocortisone (short-acting)
50 mg	Cortisone (short-acting)

Source: http://emedicine.medscape.com/article/2172042-overview.

16.5 Table of Tissue Samples and Informed Consents Required

Sample Type	Source	Purposes	Optional Tumor Sample Provision ICF	Optional Biological Sample Storage ICF
Tissue	Archival sample - mandatory when available	WT1 IHC/CISH IDH 1/2 mutation and MGMT Promotor Methylation Status* Retrospective biomarkers**	Required if patient undergoes medically necessary neurosurgical procedures (End of Study only)	Required for retrospective biomarkers and long term storage
Blood	Optional extra blood tests at times specified in the Schedule of Assessments	Retrospective biomarkers**	NA	Required for retrospective biomarkers and long term storage

Abbreviations: CISH = chromogenic in situ hybridization; ICF = informed consent form; IDH = isocitrate dehydrogenase; IHC = immunohistochemistry; MGMT = O6-methyl-guanyl-methyl-transferase; WT1 = Wilms' Tumor 1
*WT1 IHC/CISH IDH 1/2 mutation and MGMT Promotor Methylation Status mandatory test if tissue samples available; therefore, these tests are covered by the main study informed consent form.
** Retrospective biomarkers – optional test on tissue and blood samples also requiring consent for long-term storage.

16.6 Investigator Signature Page

Protocol Title: A Randomized, Multicenter, Adaptive Phase 3 Study of DSP-7888 Dosing Emulsion in Combination with Bevacizumab versus Bevacizumab Alone in Patients with Recurrent or Progressive Glioblastoma following Initial Therapy

Protocol Number: BBI-DSP7888-201G

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), cGCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Boston Biomedical, Inc., and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Boston Biomedical, Inc., and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Boston Biomedical, Inc., to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution