WINSHIP PROTOCOL #: Winship5070-20

TITLE: A Phase 1 / 2 study of Visudyne (liposomal verteporfin) in persons with recurrent high grade EGFR-mutated glioblastoma.

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TABLE OF CONTENTS

TABLE OF CONTENTS **2**

1. STUDY SUMMARY **4**

1.1 Synopsis 4
1.2 Schema 5
1.3 Schedule of Activities 8

2. OBJECTIVES AND ENDPOINTS **10**

3. BACKGROUND **11**

3.1 Study Rationale 11
3.2 Clinical experience 12
3.3 Potential Risks and Benefits 12

4. STUDY DESIGN **14**

4.1 Overall Design 14
4.2 Justification for Dose 15

5. STUDY INTERVENTION **16**

5.1 Agent Administration (or Study Intervention Administration) 16

5.1.1 STUDY INTERVENTION DESCRIPTION **16**

5.1.2 DOSING AND ADMINISTRATION **16**

5.1.3 DEFINITION OF DOSE-LIMITING TOXICITY **17**

5.1.4 DOSE MODIFICATIONS **18**

5.2 Agent Preparation/Handling/Storage/Accountability 19

5.2.1 ACQUISITION AND ACCOUNTABILITY **19**

5.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING **19**

5.2.3 PRODUCT STORAGE AND STABILITY **19**

5.2.4 PREPARATION **20**

5.3 General Concomitant Medication and Supportive Care Guidelines 20

5.3.1 RESCUE MEDICATIONS & SUPPORTIVE CARE **20**

5.4 Duration of Therapy (Study Timelines) 21
5.5 Duration of Follow Up 21
5.6 Discontinuation of Study Intervention 22
5.7 Sharing of Results with Participants 23

6. STUDY ASSESSMENTS AND PROCEDURES **24**

6.1 Schedule of Study Procedures 24
6.2 Description of study procedures 25

7. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES **27**

7.1 Biomarker Plan 27

8. STUDY POPULATION **29**

8.1 Inclusion Criteria....29
8.2 Exclusion Criteria....30
8.3 Vulnerable Populations* N/A ☒....31

9. REGISTRATION PROCEDURES....32

9.1 Local Winship Procedures....32
9.2 Recruitment / Enrollment....32
9.3 Withdrawal of Participants....32

10. MEASUREMENT OF EFFECT....34

11. STATISTICAL CONSIDERATIONS....36

11.1 Sample Size....36
11.3 Statistical methods....36

11.3.1 SAFETY ANALYSES....36

11.3.2 BASELINE DESCRIPTIVE STATISTICS....36

12. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS....39

12.1 Comprehensive Adverse Events and Potential Risks List....39
12.2 Definition of Adverse Events (AE)....39
12.3 Definition of Serious Adverse Events (SAE)....39
12.4 Classification of an Adverse Event....40
12.5 Adverse Event and Serious Adverse Event Reporting....41

13. DATA MANAGEMENT/ REGULATORY REQUIREMENTS....47

13.1 Data Reporting....47

13.1.1 SOURCE DATA AND DOCUMENTS....47

13.2 Data and Safety Monitoring Plan....47

14. ETHICS AND PROTECTION OF HUMAN SUBJECTS....49

14.1 Ethical standard....49
14.2 Institutional review board....49
14.3 Informed Consent Process....49
14.4 Process to Document Consent in Writing....50
14.5 Setting....50
14.6 Resources Available....50
14.7 Provision to Protect the Privacy Interests of Participants....50
14.8 Economic Burden to Participants....51
14.9 Research use of stored samples, specimens, or data....51
14.10 Multi-Site Research when Emory is the Lead Site*N/A ☒....51

15. REFERENCES....52

APPENDIX A PERFORMANCE STATUS CRITERIA....54

APPENDIX B ABBREVIATIONS AND DEFINITION OF TERMS....55

1. STUDY SUMMARY

1.1 Synopsis

Title:	A Phase 1 / 2 study of Visudyne (liposomal verteporfin) in subjects with recurrent high grade EGFR-mutated glioblastoma.
Study Description:	Accelerated dose-escalation phase 1 clinical trial of liposomal verteporfin for subjects with recurrent, EGFR-positive glioblastoma followed by expansion of maximum tolerated dose cohort into first stage of a Simon 2-stage phase 2 trial.
Objectives:	Primary Objective (phase 1): To characterize toxicity and determine the Maximum Tolerated Dose (MTD) of liposomal verteporfin given on a weekly schedule. Secondary Objectives: progression-free survival (PFS), response rate (RR) - Primary Objective (phase 2): To determine PFS of participants treated with liposomal verteporfin at the MTD. Secondary objectives: Response rate (RR), toxicity
Endpoints:	Phase 1: Toxicity, PFS, RR Phase 2 : PFS, Toxicity, RR
Study Population:	Subjetcs with EGFR+ GBM recurrent after adequate primary treatment.
Phase:	1 / 2
Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute, Phase 1 Unit
Description of Study Intervention:	liposomal verteporfin administered IV weekly until progression or unacceptable toxicity. Cycle 1 is weekly. Subsequent cycles are 5 out of 6 weeks.
Study Duration:	2 years
Participant Duration:	6-18 Weeks (or more)

1.2 Schema

PHASE 1/2:

Eligible participant has:

- Histologically proven glioblastoma
- Documented EGFR mutation or amplification of tumor
- Radiographic progression following completion of primary treatment
- 3+ months since completion of primary treatment.
- Participants who have received bevacizumab must have progressed while on bevacizumab.
- Participants thought to have benefit from ongoing bevacizumab may continue bevacizumab during study treatment.
- ECOG PS 0-3

Study design:

- Dose cohorts start at 0.3 mg/kg/dose of Visudyne, weekly.
- First cohort has 3 participants to establish pharmacokinetic data
- Subsequent cohort has 1 (or more) participant until grade 2 toxicity is encountered
- Each new cohort increases dose by 100% to cohort 5 (4.8 mg/kg)
- After grade 2 toxicity or cohort 5 each cohort has 3-6 participants; escalations are then according to “modified Fibonacci” scale (50%, then 33%, then 25%)
- New dose escalation cohort does not open until necessary number of participants in prior cohort have completed a cycle.
- DLT (dose limiting toxicity) is grade 3+ toxicity thought due to Visudyne.
- If 2 of 6 participants in a cohort encounter DLT, that dose is the MTD

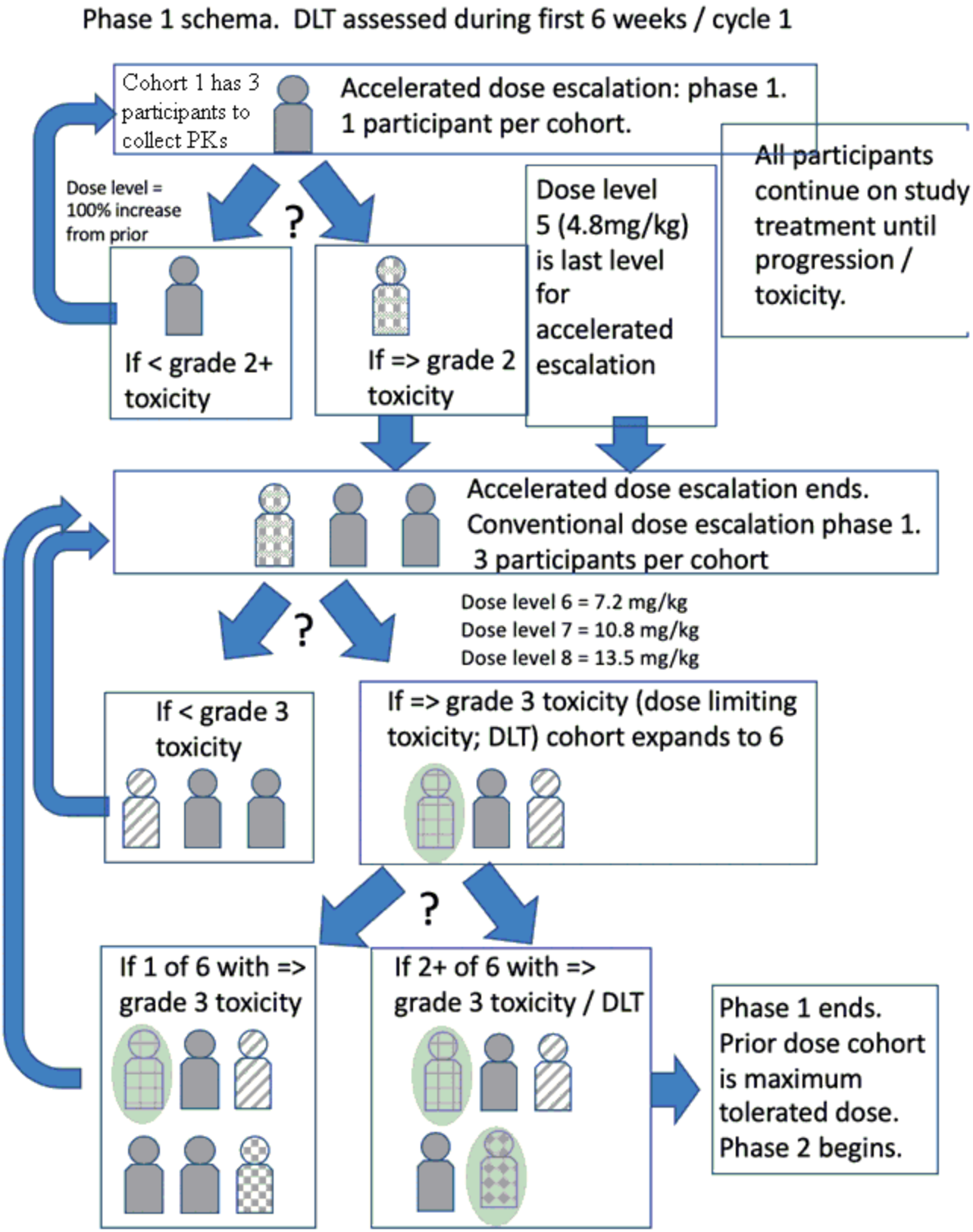
Study Treatment

- Each cycle is 6 weeks. After cycle 1 participants have 1 week off / cycle.
- Visudyne IV every 7 days at dose according to dose escalation cohort open on enrollment.
- Participants are followed weekly during cycle 1 for toxicity.
- Participants who continue to a second or subsequent cycle are evaluated every 2 weeks.
- Week 6: repeat MRI with response assessment

Study Duration

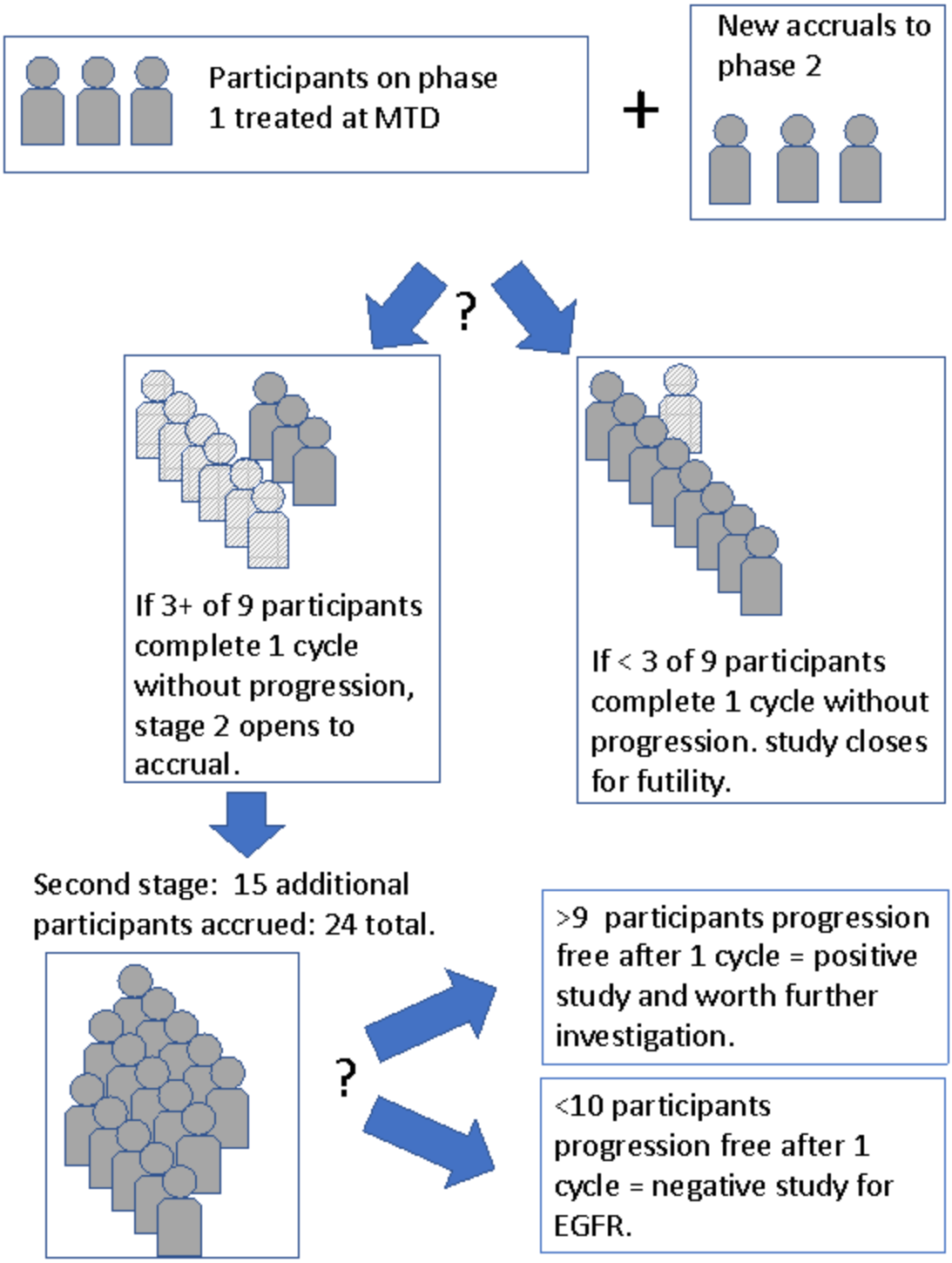
- Participants continue study treatment until there is progression, toxicity, or lack of benefit
- MRI repeats every 6 weeks. After 18 weeks (3 cycles) MRI interval may be increased to 12 weeks at discretion of treating physician.
- Toxicity assessment continues every 2 weeks. After 18 weeks toxicity assessment may be increased to every 3 weeks at discretion of treating physician.

- If 3 or more of 9 participants (at MTD or higher) have PFS > 6 weeks, second stage of 15 additional participants opens to accrual for 24 participants total.


Phase 1 schema. DLT assessed during first 6 weeks / cycle 1
Cohort 1 has 3 participants to collect PKs
Accelerated dose escalation: phase 1. 1 participant per cohort.
All participants continue on study treatment until progression / toxicity.
Dose level = 100% increase from prior
?
If < grade 2+ toxicity
If => grade 2 toxicity
Dose level 5 (4.8mg/kg) is last level for accelerated escalation
Accelerated dose escalation ends. Conventional dose escalation phase 1. 3 participants per cohort
?
Dose level 6 = 7.2 mg/kg
Dose level 7 = 10.8 mg/kg
Dose level 8 = 13.5 mg/kg
If < grade 3 toxicity
If => grade 3 toxicity (dose limiting toxicity; DLT) cohort expands to 6
?
If 1 of 6 with => grade 3 toxicity
If 2+ of 6 with => grade 3 toxicity / DLT
Phase 1 ends. Prior dose cohort is maximum tolerated dose. Phase 2 begins.

Phase 2 schema. DLT assessed during first 6 weeks / cycle 1

First stage: 9 participants accrued



Accelerated Dose Escalation Schedule (liposomal verteporfin)	
Dose Level	liposomal verteporfin (liposomal verteporfin); IND TBD
Level 1	0.3 mg/kg/week
Level 2	0.6 mg/kg/week
Level 3	1.2 mg/kg/week
Level 4	2.4 mg/kg/week
Level 5	4.8 mg/kg/week Accelerated escalation ends with this dose level
Level 6	7.2 mg/kg/week
Level 7	10.8 mg/kg/week
Level 8	13.5 mg/kg/week
• NOTE: This dose escalation schedule is the initial, accelerated dose escalation. Each dose level is double the preceding. If toxicity is encountered, or after dose level 5, dose escalations will proceed according to a modified Fibonacci schema (50%, 33%, 25%)	

1.3 Schedule of Activities

	Screening[a]	**Cycle1**						**Cycle2+**[e]						**EOT**
Procedures	Day -7 to -1	**Enrollment/Baseline Cycle 1**, Day 1	**Study Visit 2** Cycle 1 Day 8 +/-1 day	**Study Visit 3** Cycle 1 Day 15 +/- 1 day	**Study Visit 4** Cycle 1Day 22 +/-1 day	**Study Visit 5** Cycle 1Day 29+/-1 day	**Study Visit 6** Cycle 1Day 36 +/-1 day	**Study Visit 7**[e] **Cycle 2+** Day 1 +/-1 day	**Study Visit 8** Cycle 2+ Day 8+/-1 day	**Study Visit 9** Cycle 2+ Day 15 +/-1 day	**Study Visit 10** Cycle 2+ Day 22+/-1 day	**Study Visit 11** Cycle 2+ Day 29 +/- 1 day	**Study Visit 12** Cycle 2+ Day 36 +/-1day	**EOT**
Informed consent	X													
Demographics	X													
Medical history	X													
Administer study intervention		X	X	X	X	X	X	X	X	X	X	X		
Con. medication review	X	X----------X												
Physical exam	X	X	X	X	X	X	X	X		X		X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X		X		X		X		X		X		X
Hematology, coagulation parameters[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory test (CMP)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test	X	X												
AEs review and evaluation	X	X----------X												X
Radiologic/Imaging assessment [a,d]	X						X						X	
Other (pharmacokinetics)[f]	X	X												
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. All screening procedures should be completed within 7 days of Day 1 unless specified otherwise prior to initiation of therapy as applicable, except for baseline imaging (up to 14 days allowed) unless otherwise specified. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated.
b. Pregnancy test will be performed at Screening and on C1D1. Pregnancy tests performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated.
c. Hematology and Clinical chemistry Laboratory tests are listed in Protocol Section 6.2
d. MRI will be repeated after 1 cycle (6 weeks) and assessed for response or progression. MRI then continues every 6 weeks. After 18 weeks (3 cycles) the MRI interval can be increased to every 12 weeks at the treating physician's discretion.
e. Note that with cycle 2+ treatment is 5 out of every 6 weeks. The week off is at the discretion of the patient. Scheduled actions that fall on a day which has been chosen as the off day will not be done.
f. See section 7.1 for Biomarker plan. PK samples to be collected Cycle 1 Day 1 and Cycle 1 Day 2.

2. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary (phase 1)	
To evaluate the safety and tolerability of successively higher doses of liposomal verteporfin and determine the maximum tolerated dose (MTD) in study participants with recurrent EGFR+ GBM.	• Toxicity as graded by NCI CTCAE v. 5.0
Secondary (phase 1)	
To evaluate the anti-tumor activity of liposomal verteporfin by assessing progression-free survival (PFS) and overall survival (OS). To describe the response rate of EGFR+ GBM in study participants treated with liposomal verteporfin To describe pharmacokinetics of liposomal verteporfin administered on a weekly schedule.	• PFS as per RANO criteria for MRI evaluation of GBM. • RR as per RANO criteria for MRI evaluation of GBM. • Overall Survival • liposomal verteporfin blood levels at timepoints following administration.
Primary (phase 2)	
To evaluate the anti-tumor activity of liposomal verteporfin by assessing progression-free survival (PFS) and overall survival (OS). To describe the response rate of EGFR+ GBM in study participants treated with liposomal verteporfin	• PFS as per RANO criteria for MRI evaluation of GBM. • RR as per RANO criteria for MRI evaluation of GBM. • Overall Survival
Secondary (phase 2)	
To evaluate the safety and tolerability of successively higher doses of liposomal verteporfin in study participants with recurrent EGFR+ GBM.	• Toxicity as graded by NCI CTCAE v. 5.0

3. BACKGROUND

Recurrent glioblastoma. There is currently no standard treatment for patients with recurrent or progressive GBM[1]. No intervention has been proven to improve survival. Bevacizumab was approved for the treatment of patients with recurrent GBM by the FDA on the basis of response rate, and bevacizumab can palliate the symptoms of recurrent tumor or radiation necrosis. It has been recently recognized that although bevacizumab can prolong progression-free survival (presumably by suppression of edema), it does not improve overall survival. A phase 3 randomized comparison of nivolumab with bevacizumab for subjects with recurrent GBM found no difference between the two[2], and a subsequent trial of lomustine with or without bevacizumab also found no difference[3]. Non-bevacizumab therapies in these studies conferred a PFS of 1.5 months.

A different retrospective study found no overall survival benefit to the addition of chemotherapy to bevacizumab in this context, concluding second line chemotherapy for GBM to be ineffective and toxic.[4] A review of phase II clinical trials for bevacizumab refractory GBM found that among the 16 studies reviewed, no approach showed benefit, with a median OS of only 3.6 months.[5] The authors of this review conclude "the optimal treatment for disease progression after bevacizumab has yet to be elucidated and no chemotherapeutic agent has been shown to salvage patients after bevacizumab failure". As regards subjects who had progressed through bevacizumab a meta-analysis found median PFS of 1.6 months for those who stopped bevacizumab treatment vs 2.8 for those who continued.[6] A subsequent randomized phase 2 study found a PFS of 1.8 months for persons continuing bevacizumab vs 2 months for those who stopped.[7]

An important note: some patients thought to have recurrent GBM, who are treated with bevacizumab, do extremely well for many months, with dramatic MRI responses and clinical benefit. This is thought to largely be due to the efficacy of bevacizumab in reversing radiation-related brain necrosis.[8] All patients with recurrent glioblastoma have received radiation with primary treatment, and radiation related brain changes are common in this population. It is difficult to distinguish radiation related brain changes from recurrent tumor on MRI.

YAP and the Hippo pathway. For cancer in general and glioblastoma in particular, there is great interest in identifying cellular pathways vital to the tumor but dispensable for normal cells. Targeted therapies interfering with such pathways can suppress or kill pathway-dependent cancer cells with minimal impact on normal tissues. One candidate for such a pathway is the Hippo-YAP pathway, described as "a newly delineated signaling module that drives cell proliferation and survival in a large fraction of tumors and yet seems to play a minimal role in adult tissue homeostasis."[9] This pathway is important for embryonic development but can be reactivated in tumors to drive embryo-like cell proliferation. The transcriptional activator YAP is overexpressed in a variety of cancers[10] including high grade gliomas, among which 100% of grade 3 and 80% of grade 4 studied overexpressed YAP.[11] Genetic or pharmacologic disruption of YAP disrupts the cancer cells driven by it.[12-14] It has been shown that YAP is the downstream effector of mutant or amplified EGFR, which has been recognized to occur in 57% of glioblastoma.[15] YAP (and related kinase TAZ) in turn upregulate EGFR, producing a runaway feedforward loop that stimulates cell growth.[16]

3.1 Study Rationale

Verteporfin. A screen for molecules interacting with and disrupting YAP turned up verteporfin, a porphyrin pharmacologic agent used by ophthalmologists with photodynamic therapy to treat choroidal

neovascularization.[17] The interaction of verteporfin and YAP is distinct from its role as a photosensitizer and does not require light. The ability to disrupt YAP is specific to verteporfin, and is present to a much lesser degree in other porphyrins. Verteporfin alone is poorly soluble, and is used clinically as a liposomal preparation under the brand name Visudyne. Visudyne is FDA approved and has been used clinically for over a decade to treat macular degeneration and other vascular diseases of the eye. There are published clinical trials studying Visudyne at higher doses with PDT to treat cancers of the skin and pancreas.[18,19] There is not published data for repeated human dosing of verteporfin, but pharmacokinetic studies show the drug to be rapidly cleared, suggesting dosing intervals of a week or more should be safe.[20] Verteporfin and porphyrins in general achieve high levels in the brain, and are avidly taken up in vitro by tumor cells of various types.[21] Work from the Read lab has shown that GBM cells (YAP-positive and negative) likewise take up verteporfin but the inhibitory effect of verteporfin is specific for YAP overexpressing cells.[16] A previous phase 0 study by our group showed that in study participants undergoing planned resection of GBM who received a preoperative dose of liposomal verteporfin, intraoperatively and postoperative verteporfin could be visualized in the tumor – it crosses the blood brain barrier and accumulates in gliomas.[22]

3.2 Clinical experience

Liposomal verteporfin dose. The clinically used dose of Visudyne (liposomal verteporfin) for eye PDT is 6 mg/m2 or 0.15 mg/kg for an 80 kg person. In the phase 0 study, we used 0.3 mg/kg x 1 dose before surgery.[22] The highest published human dose is 0.4 mg/kg in a phase 1 study of PDT for pancreatic cancer. Significantly higher doses have been given to animals with minimal toxicity. Published doses include 10 mg/kg/day for dogs and 25mg/kg/day for rats.[23]The 2016 product monograph states "There was no significant systemic toxicity observed in these acute studies in animals that received the lipid formulation, either with or without verteporfin. Rats were dosed up to 100 mg/kg and dogs up to 20 mg/kg of verteporfin.".
We will determine the tolerable and effective weekly dose of liposomal verteporfin in the course of this clinical trial.

3.3 Potential Risks and Benefits

In animal toxicology studies, toxicity from liposomal verteporfin is generally related to light sensitization. Animals not exposed to light experienced hematologic effects at high doses, which also occurred in animals treated only with the lipid vehicle and no verteporfin. From the Investigators brochure[23]:

In general, the acute and light-dependent toxicity of verteporfin was characterized by dose dependent localized deep-tissue damage as a consequence of the pharmacologic effect of PDT with verteporfin. Toxicity observed following multiple doses of verteporfin without light were associated mainly with effects on the hematopoietic system. The extent and severity of these effects were consistent among all studies and were dependent on drug dose and dosing duration. Hematopoietic effects were also observed in animals treated with multiple doses of the lipid formulation without verteporfin.

Light sensitivity. Liposomal verteporfin greatly increases light sensitivity. Recommendations for persons treated with liposomal verteporfin and photodynamic therapy are that " patients should wear dark sunglasses, a wide-brimmed hat, and long pants and sleeves when outdoors…. Based on the findings in the placebo-controlled trials, expert opinion suggests that verteporfin treated patients should adhere to these photosensitivity precautions for 2 days after treatment."[26]

Animals treated with higher doses of liposomal verteporfin and exposed to simulated sunlight suffered severe burns. From the Investigators Brochure section 4[23]:

In acute toxicity studies in rats and dogs, verteporfin was administered intravenously and the hindlimb skin was exposed to filtered light of 687-713 nm, wavelengths similar to those used to activate the drug in humans. The drug dose ranged from 0 to 100 mg/kg and light dose ranged from 0 to 100 J/cm2. Effects without light were also assessed. The acute toxic effect was localized deep-tissue damage that only occurred after light application and which was related to the dose of both drug and light.

Verteporfin was evaluated in mice exposed to 5 minutes of whole-body simulated sunlight to assess the duration of skin photosensitivity. No skin photoreactivity was detected in mice given verteporfin at 2 mg/kg and exposed to light at 3, 24 or 48 hours after dosing. At a dose of 10 mg/kg, severe changes to the skin resulting in the formation of large eschars were observed in mice exposed to light 3 hours after drug administration

Eye toxicity was less serious in animal studies .
A study of ocular sensitivity to ambient light was performed in normal dogs to determine the effects of exposure to strong sunlight 24 hours after intravenous administration of verteporfin. Although significant skin toxicity was observed, no ocular toxicity (as assessed by histopathology) was observed at the highest drug dose tested (approximately 130 times the dose used for treatment of ocular indications) [25]

Hematopoetic toxicity. Hematopoetic toxicity was seen at high doses in animal studies, though not in human studies.
In a 28-day study in rats, verteporfin was associated with transient losses in body weight and mild dose-related anemia associated with changes in the hematopoietic system at doses of 2, 10, or 25 mg/kg/day. Vascular irritation at the injection site was also observed at these doses. In dogs given 10 mg/kg/day every day for 2 weeks, microscopic changes that correlated with a decrease in erythrocyte parameters were observed in the liver, spleen and bone marrow. No treatment-related effects were seen at 5 mg/kg/day, a repeated daily dose 33 times greater than used as a single dose for AMD treatment.[25]

Allergic reaction.

Extravasation risk. Human and animal studies both noted the risk of tissue damage due to extravasation. In human clinical experience, extravasation events produced itching and sunburn like changes, and may have been due to phototoxicity.[26]

4. STUDY DESIGN

See study schemas in section 1.2.
This is a phase 1 / 2 study of Visudyne (liposomal verteporfin) for persons with recurrent EGFR-positrive glioblastoma. The study uses an accelerated dose escalation phase 1 components, transitioning to a Simon 2-stage phase 2 component. Because preclinical studies found a very low toxicity for animals (there is no published LD50 or LD10 for Visudyne) accelerated dose finding will allow us to quickly ramp up the dose by 100% increments to one which will hopefully be effective against GBM. As per standard accelerated phase 1 protocol, once there is an instance of grade 2 toxicity thought due to drug, accelerated escalation stops and subsequent escalations are smaller. Accelerated escalation will also stop after dose level 5 (4.8 mg/kg) with subsequent smaller escalations for dose levels 6, 7 and 8.
Once the MTD is found, that cohort expands into the first stage of a 2-stage phase 2 study, the primary endpoint being progression free survival at 6 weeks (1 cycle). Participants in the phase 1 study who were treated at or higher than the MTD will count towards accrual targets for the stage 1 phase 2.
In the phase 2 study, 3 or more of the 9 participants in the first stage must be progression free at 6 weeks for the study to open the second stage. If the second stage opens (and at this point we would need to see additional funding / continued drug supply) 15 additional participants will be accrued. Of the final 24 participants 9 or more must be progression free at 6 weeks for liposomal verteporfin to be worth further evaluation in EGFR+ GBM

4.1 Overall Design

Phase 1 design.
Background: accelerated titration phase 1 design. Because of the very low toxicity of liposomal verteporfin in animal studies, this phase 1 study uses an accelerated titration phase 1 design as laid out by Simon et al.[27] Following an initial cohort of 3 patients at the first dose level to establish baseline pharmacokinetic parameters of exposure, the accelerated design enrolls only one participant per dose level until one participant exhibits grade 2 or higher toxicity during their first course of treatment. At that time, the escalation plan switches to a standard 3+3 design. That is, two additional patients are accrued at the dose that triggered the switch, and three to six patients are treated in that and each subsequent cohort. This structure is intended to speed evaluation of low dose levels with probable low toxicity and low activity. Since it was proposed in 1997, many phase 1 studies have used this design. An evaluation of these studies showed that as compared to conventional phase 1 structure, the accelerated design allowed exploration of more dose levels and had fewer participants treated at inactive low doses.[28]
FDA reviewers asked that accelerated dose escalation stop at dose level 5 (4.8 mg/kg) regardless of toxicity encountered. Dose level 6, 7 and 8 will switch to a standard 3+3 design and use more modest escalations.

Overview: phase 1. Each cohort will use a successively higher dose. The next higher cohort will not open until the minimum necessary number of participants in the prior cohort become assessable for toxicity by completing one 6 week cycle. The PI or designee must obtain approval from the DSMC for dose escalation. The PI will provide an update on all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned.

With the exception of the first cohort at 0.3mg/kg/week with 3 participants, accelerated dose escalation cohorts will have 1 minimum participant and will escalate by 100% each cohort. When a participant encounters grade 2 toxicity, escalations will decrease to 50%, then 33% then 25% per cohort and each cohort

will have a minimum of 3 participants. When a participant encounters grade 3 or 4 (dose limiting) toxicity the number of participants in that cohort will increase to 6. If 2 of 6 participants encounter DLT then the phase 1 part of this study ends and the dose of the prior cohort is the maximum tolerated dose. If 1 of 6 participants encounters DLT the next cohort will open at a 25% dose increase.

When the phase 1 portion of this study has determined the MTD, this cohort will be expanded to form the first stage of a Simon 2-stage phase 2 clinical trial, with primary endpoint progression-free survival at 6 weeks.

Phase 2 design / statistics

The phase 2 component of this study is a 2-stage phase 2 clinical trial as proposed by Simon et al.[29] The 2 stage studies are intended to limit continued enrollment of participants to a study which is unlikely to meet its endpoint. In 2 stage phase 2 trials, a first stage of enrollments is assessed for a predetermined endpoint, which for this study is percentage of participants who remain progression free after 6 weeks on study. . If it is statistically unlikely that additional enrollments would push the trial to achieve the endpoint, the study ends. If achievement of the desired endpoint was adequately frequent among participants in the first stage, a second larger stage opens to enrollment, with the cumulative result of the two stages a statistically significant result.

The phase 2 component of this phase 1 / 2 study is structured as a Simon 2 stage phase 2 study with the primary endpoint of progression free survival. Recent randomized studies found that persons with recurrent GBM receiving non-bevacizumab therapies had a PFS of 1.5 months for both nivolumab[2] and lomustine[3]. As regards patients who had progressed through bevacizumab a meta-analysis found median PFS of 1.6 months for those who stopped bevacizumab treatment vs 2.8 for those who continued.[6] A subsequent randomized phase 2 study found a PFS of 1.8 months for subjects continuing bevacizumab vs 2 months for those who stopped.[7]

Participants in the phase 1 component of this study who are or were treated at the MTD cohort will count toward the phase 2 stage 1 accrual target of 9. Additional participants will be accrued to this target until there are 9 evaluable participants.

With 80% power, a Type I error of 0.05, and a 50% good non-progression rate vs. 25% poor non-progression rate at 6 weeks (1 cycle), the total sample size needed for a Simon 2-stage is 24 (9 in Stage 1, 15 in Stage 2). In the first stage, 3 or more of the 9 participants (in the MTD cohort) must be progression free through 6 weeks for the study to proceed on to the second stage. If 2 or fewer achieve this, the study will close for futility. If 3 or more achieve this, stage 2 will commence and 15 additional participants will be accrued. A formal statistical plan will be produced by Biostats before this protocol is submitted for IRB review.

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4.2 Justification for Dose

Dose. Verteporfin has been used clinically for more than a decade. For photodynamic treatment the drug is administered intravenously in advance of light application to the treated area, usually the eye. The standard dose for photodynamic treatment (PDT) of the eye is 0.15 mg/kg for an 80 kg person. Higher doses have been used in clinical trials. A large phase 2 study of PDT for skin tumors used 14 mg/m2 or 0.35 mg/kg and a phase 1-2 study of PDT for pancreatic cancer used 0.4 mg/kg. [18,19] A phase 1 study of verteporfin looked at some doses even higher than that, up to 0.5 mg/kg.[14] Intravenous liposomal verteporfin was well tolerated at all doses, with no emergent toxicities at higher doses. Toxicities observed were due to local irritation at the site of PDT. Significantly higher doses have been given to animals with minimal toxicity.[24] Published doses include 10 mg/kg/day for dogs and 25 mg/kg/day for rats. There is no published LD50 or LD10 for verteporfin in any animal. It is not known what dose of verteporfin is effective against GBM, if it is effective at all. The completed phase 0 study discovered verteporfin in tumor resected from study participants who had received a single

preoperative dose of 0.3 mg/kg liposomal verteporfin. This study will start with 0.3 mg/kg/dose and escalate according to a phase 1 scheme.

Schedule. PDT is generally given once, with repeat treatments done two or 3 months later if needed – this because of the phototoxicity to the eye or other treated tissues. There is not experience with weekly or other short interval repeat dosing of verteporfin in humans. A pharmacokinetic study in humans found that because of the short (5-6 hour) half life of verteporfin, dose intervals of a week or more should be safe.[20] This study will use weekly verteporfin dosing.

5. STUDY INTERVENTION

5.1 Agent Administration (or Study Intervention Administration)

5.1.1 Study Intervention Description

Visudyne (liposomal verteporfin). Current information on Visudyne can be read at **http://www.bausch.com/Portals/109/-/m/BL/United%20States/Files/Package%20Inserts/Pharma/visudyne-package-insert.pdf**

5.1.2 Dosing and Administration

Reconstitution. Visudyne will be reconstituted in D5W as is standardly done for clinical use, described **http://www.bausch.com/Portals/109/-/m/BL/United%20States/Files/Downloads/ECP/Pharma/Visudyne-preparation-guide.pdf .** Reconstituted Visudyne is usually diluted with additional D5W to make a total volume of 30 cc. Because doses in this study will be higher than are currently used clinically, and more concentrated liposomal solutions might increase the risk of reaction to the liposomal component, in this study all doses will be diluted in 250 cc D5W rather than 30 cc.

Administration. Liposomal verteporfin is a vesicant. All participants in this study will receive verteporfin through a central venous access to minimize the chance of extravasation and injury. The 250 cc of D5W will be administered with an infusion pump and inline filter at the same rate as is used clinically: 3 ml / minute. It will take 83 minutes.

Premedication. Infusion related toxicity has been described for Visudyne (lipsonal verteporfin).[30,31] This is similar to that described for other liposomal drugs and can include itching, flushing, hyper or hypotension, wheezing, back pain and other symptoms beginning shortly after infusion start. Participants in this study will receive premedication with dexamethasone 4 mg po, diphenhydramine 25mg po and famotidine 20mg po in advance of treatment to decrease the chance of acute infusion-related toxicity. If encountered, infusion related toxicity may also be addressed by slowing infusion rate.

Dose escalation:

See schemas at 1.2 for dose escalation rules.

Rules for Dose Escalation and Rules for Maximum Tolerated Dose (MTD)

- One to 6 participants will be entered at each dose level until the DLT (dose limiting toxicity) dose level is determined. Assessment for DLT will be based on events that occur during the first treatment cycle (6 weeks), and is defined as the dose level at which 2 of 6 participants experience a DLT. Once the DLT dose level is defined, no additional participants will be enrolled at that dose level.
- **The PI or designee must obtain approval from the DSMC for dose escalation. The PI will provide an update on all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned**

- The dose level below the DLT dose level will be defined as the MTD level. A total of up to 9 participants may be entered at the MTD level to ascertain progression-free survival (phase 2 component). However, if ≥ 3 of the 9 enrolled participants have a DLT then the MTD level will be rejected. In this event a lower MTD level will be evaluated.

- Because of the low toxicity of liposomal verteporfin, the study will start with accelerated titration and at least 1 participant per cohort. The first cohort will use a dose of liposomal verteporfin at 0.3mg/kg/week. There must be at least 1 evaluable participant before a new dose escalated cohort can open for enrollment. Subsequent dose escalations will follow an accelerated titration design with escalations of 100% in a cohort containing at least 1 participant until any Grade 2 toxicity occurs that is possibly, probably, or definitely related to study drug**. Accelerated titration will end with dose level 5 (4.8 mg/kg)**

- Once Grade 2 toxicity occurs as defined above, or once a single participant completes a cycle at dose level 5, subsequent cohorts will be expanded to 3 participants. Dose escalations will be 50%, then 33% then 25%. At least 3 participants must be fully evaluable prior to subsequent dose escalation. Once a DLT is observed that cohort will be expanded to at least 6 participants.

- If only 1 of the 6 participants in this expanded cohort experiences a DLT, further dose escalation will occur but will be no greater than 25% of the current dose level. Dose escalation will be terminated if 2 of 6 participants at a given dose level experience a DLT. If 2 participants experience a DLT prior to completing the cohort, the DLT dose level will have been achieved, and no additional participants will be enrolled at the DLT dose level.

- Once DLT is determined, participants in that cohort may continue on study but will receive drug at the MTD, one dose cohort lower that the DLT cohort.

- The dose level below the DLT dose level will be considered the MTD level, and this cohort may be expanded to a total of 9 participants to assess whether liposomal verteporfin improves PFS.

- Dose escalations will not go higher than 13.5 mg/kg/dose. If there is no toxicity and escalations occur at 100% with cohorts 1 thru 5 and then 50%, 33% and 25% with cohorts 6,7, and 8, 13.5mg/kg will be the 8th cohort.

Dose Expansion Phase

In this study, rather than a dose expansion phase the study will convert to a phase 2 study, in hopes for more rigor as regards evaluating the therapeutic outcome of progression free survival. As noted above, after the

MTD is established, participants in the phase 1 study who were treated at or above the MTD will be counted as accruals towards the phase 2 stage 1 accrual target of 9.

In the event that there is toxicity among accruals to the phase 2 component at MTD suggesting that the dose used is too toxic and the true MTD is lower, phase 1 rules will be revisited to de-escalate the dose.

5.1.3 Definition of Dose-Limiting Toxicity

Dose limiting toxicity (DLT) : definition. The determination of DLT for the purpose of assessing dose escalation will be defined as adverse events that are judged to be drug-related during the first cycle (causality rated as possible or greater) and will be defined based on the NCI CTCAE, Version 5 as follows.

- Any Grade 3 or higher non-hematological toxicity except fatigue, nausea, vomiting, diarrhea or alopecia. However, Grade 3 nausea or vomiting with pre-medication is considered a DLT.
- Any grade 4 fatigue, nausea, vomiting or diarrhea.
- Grade 4 pain that does not remit to ≤ Grade 2 within 24 hours of treatment with opiate analgesics.
- Hypersensitivity-related toxicity of Grade 3 despite pre-medication is considered a DLT.
- Grade 4 thrombocytopenia (< 25,000/µL), neutropenia (< 500/µL) or anemia (< 6.5 g/dL) on the next scheduled dosing day
- Grade 3 thrombocytopenia (<50,000) with significant bleeding is a DLT.
- Any febrile neutropenia (defined as temperature ≥ 38.5 C and ANC < 1000)
- Persons with progressive GBM may have symptoms due to their tumors. This can include seizure, intratumoral bleeding, and altered mental status. It is left to the investigator to decide if symptoms of these sort are due to study drug, and so count as toxicity, or due to progressive brain tumor, in which case they do not count as toxicity.

Toxicity	**Escalation Decision Rule**
0 out of 1	Accelerated dose escalation continues. Next cohort of 1 participant is at 100% escalation up to dose level 5 (4.8 mg/kg)
Grade 2+ in 1	Accelerated dose escalation ends. This and subsequent cohorts expand to 3 participants. Dose escalations proceed at 50%, then 33% then 25%
Grade 3+ (DLT) in 1	Accelerated dose escalation ends. This cohort expands to 6 participants.

Grade 3+ (DLT) in 1 of 6	Accelerated dose escalation ends. Subsequent cohorts are 3-6 participants. Dose escalations proceed at 25%
Grade 3+ (DLT) in 2 of 6	Dose is too toxic. No further dose escalations. Prior dose level is deemed MTD and phase 2 component of study begins .

5.1.4 Dose Modifications

Grade 2 toxicity. Grade 2 toxicity thought to be related to liposomal verteporfin should be managed supportively. At the discretion of the investigator grade 2 toxicity may prompt a 25% dose reduction for the next and subsequent doses of liposomal verteporfin, or the participant may be treated at the prior lower dose level for subsequent doses. Note that an occurrence of grade 2 toxicity during cycle 1 would prompt a switch from accelerated dose escalation (1 per cohort) to standard dose escalation (3 pwer cohort).

Grade 3 or 4 toxicity. For grade 3 or 4 toxicity all treatment will be held until toxicity improves to grade 2 or less. Liposomal verteporfin will restart at the prior lower dose level for subsequent doses. If toxicity has not resolved within 14 days the participant will discontinue study treatment. If the treating physician feels the risk of recurrent toxicity is too great even at reduced dose, the participant will leave study . Note that grade 3 or 4 toxicity may count as DLT if it occurs during the first cycle.

5.2 Agent Preparation/Handling/Storage/Accountability

5.2.1 Acquisition and accountability

The study drug provided for this study will be used only as directed in the study protocol. The Winship IDS (Investigational Drug Service) personnel will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.
Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.
The Drug Accountability Log may record specifics to study drug dispensation such as:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.
• The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.
Drug accountability will be noted by the field monitor during site visits and at the completion of the study.
The study drug supply will be disposed of as per Winship's Investigational Pharmacy (IDS) SOP

5.2.2 Formulation, Appearance, Packaging, and Labeling

From
https://www.bausch.com/Portals/77/-/m/BL/United%20States/Files/Package%20Inserts/Pharma/visudyne-package-insert.pdf
VISUDYNE is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake (3) VISUDYNE is a reconstituted sterile solution intended for intravenous injection. (3) . Each reconstituted vial provides 7.5 mL solution containing 2 mg/mL of verteporfin. VISUDYNE (verteporfin for injection) is supplied in a single-use glass vial with a gray bromobutyl stopper and aluminum flip-off cap. It contains a lyophilized dark green cake with 15 mg verteporfin.

5.2.3 Product Storage and Stability

https://www.bausch.com/Portals/77/-/m/BL/United%20States/Files/Package%20Inserts/Pharma/visudyne-package-insert.pdf

5.2.4 Preparation

Reconstitution: Parenteral Products:
Reconstituted VISUDYNE must be stored at 20-25°C, protected from light and used within 4 hours. It is recommended that reconstituted VISUDYNE be inspected visually for particulate matter and discoloration prior to administration. Reconstituted VISUDYNE is an opaque dark green solution. Discard the unused portion.
Incompatibilities
VISUDYNE should only be reconstituted with sterile Water for Injection. Do not mix VISUDYNE in the same solution with other drugs. VISUDYNE may precipitate in saline solutions. Do not use normal saline or other parenteral solutions.
Dilution for Intravenous Infusion
Once reconstituted VISUDYNE is diluted with 5% Dextrose Injection, it should preferably be used immediately, but not exceeding 4 hours after aseptic reconstitution and dilution. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration, or leakage should not be used.

5.3 General Concomitant Medication and Supportive Care Guidelines

Concurrent Anticancer Therapy: Concurrent chemotherapy, radiation therapy, immunotherapy, or biologic therapy intended for treatment of glioma, investigational or otherwise may not be administered to study participants. Participants who are thought to require such treatment will leave study, and the circumstances requiring such treatment will be categorized as toxicity or progression as appropriate.
Allowed cancer therapy: An exception is made for the Novo-TTF device, which is an FDA approved treatment for GBM. Participants who have been using this device are not obliged to discontinue it.
Bevacizumab combination. Participants on this study may continue bevacizumab, which is not effective GBM therapy but in this context an anti-edema drug. Some patients with GBM benefit greatly from the anti-edema effect of bevacizumab and the anti-edema effect could be helpful in this study as it makes it easier to see if there is true progression. Liposomal verteporfin and bevacizumab have been used together before, but in the

context of intravitreal not intravenous bevacizumab. There have not been new or emergent toxicities seen with the addition of intravenous bevacizumab to varied other chemotherapeutics, and there is no reason to think that the combination of verteporfin with bevacizumab should present new hazards. Bevacizumab is allowed on this study because of its palliative benefit for some patients and concern that discontinuation might allow rapid recurrence of edema. Bevacizumab is not thought to contribute to any anticancer effect of liposomal verteporfin.

Supportive Care: Visudyne (liposomal verteporfin). Persons treated with liposomal verteporfin may experience photosensitivity. This can be severe. All study participants will be advised to stay out of bright sun or bright direct light, and to cover skin / use sunglasses.

Supportive care: General. Appropriate antibiotics, blood products, corticosteroids, antiemetics, anticonvulsants, fluids, electrolytes and general supportive care are to be used as necessary.

5.3.1 Rescue Medications & Supportive Care

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events until start of new antineoplastic medication or 150 days after discontinuation of study drug, whichever is sooner. Suspected SAEs will continue to be collected beyond the 150-Day safety visit. This will be done by return clinic visits, laboratory checks, and phone calls as warranted by patient status and clinical condition.

5.4 Duration of Therapy (Study Timelines)

Participants will receive verteporfin IV weekly at a dose according to their cohort. Treatment can be at 8 or 6 days to accommodate holidays.

After the first cycle of 6 weeks, participants who continue on study have 1 week off every 6 weeks. It can be any of the 6 weeks.

On followup, participants will have vital signs taken, blood tests, and toxicity assessment.

Participants will be followed weekly for toxicity for the first cycle (6 weeks) then every 2 weeks. After 3 cycles (18 weeks) the followup interval can be increased to every 3 weeks at the treating physician's discretion.

MRI will be repeated after 1 cycle (6 weeks) and assessed for response or progression. MRI then continues every 6 weeks. After 18 weeks (3 cycles) the MRI interval can be increased to every 12 weeks at the treating physician's discretion.

Participants who encounter grade III-IV toxicity related to study drug or drug administration will hold treatment until toxicity resolves to grade 2 or less. Participants who are thought to be receiving clinical benefit

from study treatment and whose toxicity resolves to grade 2 within 14 days may resume study treatment, with dose modifications if warranted. See section 8 for toxicity management / dose modification.

Missed dose / late dose. Missed doses (because of illness or weather) will not be made up. Participants will continue with next scheduled dose.

Grading of Adverse Events: Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE) http://ctep.cancer.gov/reporting/ctc.html. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

5.5 Duration of Follow Up

Patients will be followed for approximately 30 days (Safety Follow-up) after the last dose of study drug or before initiation of new antineoplastic or investigational therapy whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.
Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination.
• All patients will be contacted for survival every 12 weeks following the End of Treatment (EOT) visit.
• Immunogenicity samples will be taken as per schedule of events
Patients who have not initiated a new antineoplastic regimen will have the following assessments:
• Radiologic tumor assessments every 12 weeks (± 7 days)
• In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.6 Discontinuation of Study Intervention

Study treatment discontinuation. If a participant discontinues study treatment he or she will be followed for survival, a secondary endpoint of this study. Participants will discontinue study treatment if:

- There is clinical or radiographic evidence that ongoing study treatment is not producing benefit.
- Participants encounter non-resolving grade III-IV toxicity. These participants may resume study treatment after toxicity resolves to grade 2 or less. If toxicity does not resolve within 14 days these participants will discontinue study treatment.
- Participants cannot tolerate liposomal verteporfin infusion (allergy) even with premedications and slowed infusion.
- Participants are unable to comply with study requirements.
- Participant or physician feels that continued participation is not in the participant's best interest.

Participants who discontinue study intervention will be invited to follow for management of unresolved toxicities associated with the intervention. Some participants discontinuing study treatment may enroll on hospice; persons on hospice will not be obliged to continue follow-up in person.

5.7 Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.
Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, deidentified data and/or specimens might be provided to other researchers. In this case, information that could identify the subject will not be included

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Schedule of Study Procedures

Screening Phase

Screening procedures will be performed up to 7 days prior to initiation of therapy as applicable, except for baseline imaging (up to 14 days allowed) unless otherwise specified. All subjects must first read, understand, and sign the IRB -approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- Review of prior/concomitant medications
- Imaging by MRI or scheduling of imaging if not recent (<14 days)
- Scheduling of placement of portacath if not present
- Clinical laboratory tests for:
    - Hematology
    - Clinical chemistry
    - Coagulation parameters (PT, PTT)
    - Serum or urine pregnancy test (for women of childbearing potential)

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3). Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs, weight
- Review of prior/concomitant medications Tumor imaging (every 6 weeks, after 18 weeks (3 cycles) the MRI interval can be increased to every 12 weeks at the treating physician's discretion.)
- Review of adverse events
- Clinical laboratory tests for:
    - Hematology
    - Clinical chemistry

- Coagulation parameters
- Serum or urine pregnancy test (for women of childbearing potential) cycle 1 day 1 only

Schedule of infusion of Investigational Drug		
Week	1 -6	7-13+
Cycle	1	2+
Investigational Drug	QWeek	Qweek (5 out of 6 weeks)

End of Treatment

Study participants will continue on study treatment until progression, toxicity or withdrawal for other reasons. Participants with unresolved toxicity from study treatment will be followed to support / treat toxicities until they resolve to < grade 2.
Participants will be followed for survival until the end of the study regardless of further treatments.

6.2 Description of study procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, weekly during phase 1 component / cycle 1 (for close toxicity evaluation), Day 1 of cycle 2 and beyond, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be reported at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.
On infusion days, patients receiving treatment will be monitored during and after infusion of IP as presented in the bulleted list below.

- Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).
- Approximately 30 minutes +/- 5 minutes during the infusion (**halfway** through infusion).
- At the end of the infusion (approximately 60 minutes ±5 minutes).
- A 1-hour observation period is required after the first infusion. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry
- Coagulation parameters: Activated partial thromboplastin time and protime
- Serum or urine pregnancy test (female subjects of childbearing potential only)

Hematology Laboratory Tests	
Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Clinical chemistry (serum or plasma) Laboratory Tests	
Albumin	Glucose
Alkaline phosphatase	
Alanine aminotransferase	
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

[b] At baseline and as clinically indicated

7. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

7.1 Biomarker Plan

- Pharmacokinetics: In human studies of doses up to 0.5mg/kg, liposomal verteporfin distributes rapidly through the body over 1-3 hours after infusion and is largely cleared through the feces, with a half-life of approximately 5-6 hours.[20] . In this study, blood draws to be stored for pharmacokinetic analysis will take place at specified times following infusion among participants in the phase 1 study. In order to establish dose-exposure relationships, the first cohort will enroll 3 patients, and subsequent single patient cohorts will proceed as adverse events dictate. Blood sampling will occur in cycle 1 only, and will occur on cycle 1, days 1 and 2 only according to the following schedule:

Timepoint	**Collection**
Cycle 1, Day 1	
Pre-dose	X
End of infusion (EOI)	X
EOI + 0.5 hours (± 5 minutes)	X
EOI + 1 hour (± 10 minutes)	X
EOI + 3 hours (± 15 minutes)	X
EOI + 5 hours (± 15 minutes)	X
EOI + 7 hours (± 15 minutes)	X
Cycle 1, Day 2 (24 hours after initiation, (± 2 hours)	X

Whole blood will be collected in potassium oxalate/sodium fluoride (gray top) tubes, centrifuged, and plasma aliquoted into 1 mL volumes into cryovials for immediate freezing. Subesequent vertoporfin enantiomer analysis by HPLC per previously described methods (Houle JM, Strong A J Clin Pharmacol 2002;42:547-557) will be performed. Across patients and dose levels, plasma concentration-time curves will be generated and the following pharmacokinetic (PK) parameters generated using non-compartmental methods:

- AUC_{0-t}: area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t)
- AUC_{0-inf}: area under the concentration-time curve from time 0 to infinity
- C_{max}: maximum observed plasma concentration
- T_{max}: time to reach maximum observed plasma concentration
- λ_z: terminal-phase elimination rate constant
- $t_{1/2}$: apparent terminal elimination half-life
- CL/F: apparent total body clearance
- V_z/F: apparent volume of distribution of the terminal phase

- Tumor analysis. Participants on this study will have previously resected tumor specimens studied for YAP/TAZ expression, EGFR expression, and other aspects of the molecular phenotype which might be relevant for understanding response or nonresponse to Visduyne treatment. New research findings might warrant other studied of related molecules in tumor tissue.
  No new biopsies will be performed. Persons with documented EGFR+ GBM who do not have available tumor tissue may still participate in this study if entry criteria are met.

Specimen Collection Schedule

Please provide the type of specimen and the timepoint (study cycle/day) of each specimen collection procedure, and mark the appropriate boxes with an "X" to denote collection on that study day.

Specimen Type	**Baseline**	***[Timepoint #2]***	***[Timepoint #3]***	***[Timepoint #4]***
Specimen type #1	*X*			
Specimen type #2	*X*			

8. STUDY POPULATION

- Participants will be recruited from the neuro-oncology practices at Emory, and among interested persons who are referred for this study or who come of their own accord after learning of the study.
- **Enrollment / eligibility.** Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the patient's research chart and medical record. Studies or procedures that were performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.
- Replacement. If a participant misses 2 or more doses in the first cycle for non-toxicity reasons (e.g. car trouble) the experience of that participant cannot be used as a reason to escalate the dose. Fewer doses might mean less toxicity and then an unwarranted dose escalation. The participant who has missed 2 or more doses may continue on study but for purposes of the accrual target for that cohort, a replacement participant will be recruited. If, however, a person who misses doses encounters toxicity that toxicity does count

8.1 Inclusion Criteria

1. Diagnosis: Persons with recurrent or progressive grade 4 glioma (glioblastoma) are eligible for this study. Participants should have received standard first line therapy including radiation and temozolomide.
2. EGFR status. Eligible participants have tumors that show mutant or amplified EGFR. This determination can be made using standard of care mutation analysis panels (e.g. Snapshot). It is often assessed at diagnosis as part of standard of care.
3. Disease Status: Eligible participants must have evidence on MRI of progression. This may be as new or increased enhancement, or growth / increase in nonenhancing abnormality. Care should be taken to distinguish those with true progression from those with radiation related changes. Persons with changes in enhancement possibly due in part or in whole to late radiation effect should receive bevacizumab as standard of care, and defer study participation.
4. Anti-VEGF treatments. Participants may be receiving bevacizumab, and show progression while on bevacizumab. These participants may continue bevacizumab while on study. Persons not on bevacizumab but who would benefit from the anti-edema effect of bevacizumab should not enroll on this study but should proceed with bevacizumab alone, and defer enrollment until such time as they progress.
5. Vascular access: liposomal verteporfin is a vesicant. Participants will likely have poor veins, and will require repeated intravenous treatments. **Participants must be willing to have placed a central venous access, such as a portacath.**
6. Performance status: ECOG PS 0-3. Participants who are ECOG 2 or 3 should ideally have been in that situation for some time, and not be in the midst of rapid clinical decline.

7. Medical comorbidities (excepting neurological) must be grade 2 or less if graded as toxicity. Examples:
    - Hemoglobin >8. Platelets > 50,000
    - Creatinine < 3x upper limit of normal
    - AST and ALT < 5x upper limit of normal
8. Eligible participants may have grade 3 neurologic comorbidities (for example aphasia, ataxia) arising as a consequence of brain pathology.
9. Male/Female 18 years or older.
10. Life expectancy: participants should be reasonably expected to be able to complete 6 weeks (1 cycle) of treatment on study before death or worsening of PS to 4 or 5.
11. Other anti-cancer medical treatments. Treatments in this category include chemotherapy and non-bevacizumab therapies. 7 days must have elapsed since discontinuation of prior chemotherapeutic treatments for glioma and study treatment. Participants may have had any number of prior treatments.
12. Radiation. All participants on this study must have had prior radiation to the brain. Radiation must have been completed 90 days prior to first study treatment.
13. Surgery. 21 days must have elapsed since prior major surgery.
14. Novo-TTF. Participants already using a Novo-TTF (Optune) device and who wish to continue may do so.
15. Informed Consent: All participants must sign a written informed consent.
16. The effects of study drugs used in this study on the developing human fetus are unknown. For this reason, female of child-bearing potential (FCBP) must have a negative serum or urine pregnancy test prior to starting therapy.
17. FCBP and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and 8 weeks after. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation . A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months..

8.2 Exclusion Criteria

1. Persons who are deemed to have progression on clinical grounds only (new symptoms, declining PS) are ineligible. In the absence of MRI change one cannot be confident that clinical deterioration is a direct result of tumor progression, and could be due to intercurrent illness.

2. Persons with edema which might be due to late radiation effect, not true progression, should receive bevacizumab as standard of care, and defer study participation. If (short-term) followup imaging shows reduction of edema and also progression of tumor, these persons are eligible (and should continue bevacizumab).

3. Pregnancy or Breast-Feeding: Pregnant or breast-feeding women will not be entered on this study.

4. Comorbidities: Participants may not have any baseline comorbidities or laboratory abnormalities which would be of grade 3 or worse if graded as toxicities by CTCAE (excepting alopecia). An exception is made for neurologic comorbidities (e.g. ataxia, aphasia) arising as a consequence of the brain tumor; symptoms severe enough to warrant medical treatment as is offered on this study are by definition grade III.

5. Persons who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are ineligible.

6. Illness or any other circumstances (as defined by the investigator), which would preclude safe performance of study procedures or compromise the ability of the patient to consent to study.

7. Persons with hereditary porphyria are ineligible.

8. Persons in need of emergency surgery are ineligible.

8.3 Vulnerable Populations* N/A ☒

9. REGISTRATION PROCEDURES

Enrollment depends on how many phase 1 study participants enroll before the MTD is determined. See section 12.

9.1 Local Winship Procedures

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

9.2 Recruitment / Enrollment

- Participants will be recruited from the neuro-oncology practices at Emory, and among interested persons who are referred for this study or who come of their own accord after learning of the study.

- Participants will not be paid. They may be provided dark glasses for eye protection. There will not be funds to defray expenses for travel or other expenses incurred by participants.

Enrolling a subject requires careful screening and determination of eligibility. Insofar as is possible, study candidates should not sign consent unless they are thought to meet entry criteria. Subjects who consent to participate in the clinical trial, and who are later found to not meet one or more criteria required for participation in the trial during the screening procedures, will not be enrolled into the study and are considered screen failures. All subjects which have signed informed consent, but were then deemed ineligible will be recorded in a log with the reason of ineligibility and their enrollment status will be updated in OnCore. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes demography, informed consent date, screen failure details, eligibility criteria, study discontinuation date, adverse events and any serious adverse event (SAE)."

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator. When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and on treatment status.

9.3 Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

Replacement.

- In the phase 1 portion of this study, if a participant misses 2 or more doses in the first cycle for non-toxicity reasons (e.g. car trouble) the experience of that participant cannot be used to gauge toxicity. The participant who has missed 2 or more doses may continue on study but for purposes of the accrual target for that cohort, a replacement participant will be recruited.
- Subjects who sign the informed consent form but do not receive the study intervention may be replaced.
- In the phase 2 portion of this study, participants who discontinue study treatment for reasons other than progression (e.g. changed their minds) before week 6 mri are not evaluable and will be replaced.

10. MEASUREMENT OF EFFECT

EVALUATION CRITERIA

This study uses the RANO radiographic criteria for MRI response and progression. Wen, et al. [32] The RANO criteria are the latest set of peer reviewed criteria for brain tumor studies, and are designed to take into account changes in nonenhancing MRI abnormalities, which may be the predominant manifestation of GBM in persons treated with bevacizumab. Response criteria below are copied from Wen et al.

DEFINITION OF RADIOGRAPHIC RESPONSE

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy should be used for determination of progression. Table 3 lists the criteria for radiographic changes after therapy. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents, such as antiangiogenic therapies, that affect vascular permeability is particularly difficult. In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease.

All measurable and nonmeasurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Complete Response

Complete response requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; and patient must be off corticosteroids or on physiologic replacement doses only, and stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

Partial Response

Partial response requires all of the following: ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and patient must be on a corticosteroid dose not greater than the dose at time of baseline scan and is stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

Stable Disease

Stable disease occurs if the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in

corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progression

Progression is defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of nonmeasurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Patients with nonmeasurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a nonmeasurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 × 9 mm lesion [nonmeasurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (> 5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size

The first cohort will treat 3 participants to establish phramcokinetic baselines. The phase 1 will proceed with an accelerated titration design, where one patient will be treated at each dose cohort until a dose-limiting toxicity (DLT) occurs, or 2 instances of grade 2 toxicity within the first cycle.. After first DLT (or 2 grade 2), the Phase 1 design will shift to a 3+3 approach until the maximum tolerated dose (MTD) is established. With a 3+3 design, 3 patients are treated at a given dose level. If 0/3 experience a DLT, the dose escalates. If 1/3 experience a DLT, then 3 more patients will be treated at that dose level. If >1 out of 6 experiences a DLT, then the previous dose is the MTD. This Phase 1 portion will include 8 to 48 patients.
The phase 2 component of this study is a 2-stage phase 2 clinical trial as proposed by Simon et al.[29] The 2 stage studies are intended to limit continued enrollment of participants to a study which is unlikely to meet its endpoint. In 2 stage phase 2 trials, a first stage of enrollments is assessed for a predetermined endpoint, which for this study is percentage of participants who remain progression free after 6 weeks on study. If it is statistically unlikely that additional enrollments would push the trial to achieve the endpoint, the study ends. If achievement of the desired endpoint was adequately frequent among participants in the first stage, a second larger stage opens to enrollment, with the cumulative result of the two stages a statistically significant result.

This study is structured as a Simon 2 stage phase 2 study with the primary endpoint of progression free survival. Recent randomized studies found that persons with recurrent GBM receiving non-bevacizumab therapies had a PFS of 1.5 months for both nivolumab[2] and lomustine[3]. As regards persons who had progressed through bevacizumab a meta-analysis found median PFS of 1.6 months for those who stopped bevacizumab treatment vs 2.8 for those who continued.[6] A subsequent randomized phase 2 study found a PFS of 1.8 months for persons continuing bevacizumab vs 2 months for those who stopped.[7]

Participants in the phase 1 component of this study who are or were treated at the MTD cohort will count toward the phase 2 stage 1 accrual target of 9. Additional participants will be accrued to this target until there are 9 evaluable participants. With 80% power, a Type I error of 0.05, and a 50% good non-progression rate vs. 25% poor non-progression rate at 6 weeks (1 cycle), the total sample size needed for a Simon 2-stage is 24 (9 in Stage 1, 15 in Stage 2). In the first stage, 3 or more of the 9 participants (in the MTD cohort) must be progression free through 6 weeks for the study to proceed on to the second stage. If 2 or fewer achieve this, the study will close for futility. If 3 or more achieve this, stage 2 will commence and 15 additional participants will be accrued.

11.3 Statistical methods

All subjects who receive any amount of study drug will be included in the evaluation of safety and efficacy. Baseline patient characteristics will be summarized descriptively, using frequencies and percentages for categorical variables and mean, median, standard deviation, and range for numeric variables.

11.2.1 Analysis of safety endpoints

The primary endpoint for the Phase 1 portion is toxicity. Adverse event data will be described and graded per the NCI CTCAE 5.0 guidelines. For each adverse event, information to be collected includes event description, time of onset, clinician assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. Regardless of relationship, all AEs will be recorded with start dates occurring any time after patient receives any study drug until 7 (for non-serious AEs) or 100 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. Adverse events will be summarized and described within each cohort. They will initially be reviewed regardless of attribution, but also whether they are possibly, probably, or definitely related to treatment. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be related" to study treatment in the event of an actual relationship developing. The incidence of severe adverse events or toxicities will be described. We will assess the proportion of patients who experience grade 3 or higher non-hematologic toxicity. To assess tolerability, we will also capture the proportion of patients who go off treatment due to adverse events.

11.2.2 Analysis of efficacy endpoints

The primary endpoint for the Phase 2 portion of the study is progression-free survival at 6 weeks. Progression-free survival is defined as no progression within 6 weeks, where progression is determined per RANO criteria for MRI evaluation of GBM. Progression-free survival will be estimated as a binary rate, and a 95% confidence interval will be estimated using the Clopper-Pearson method.

Secondary endpoints for the Phase 2 portion of the study include response rate of EGFR+ GBM in study participants treated with liposomal verteporfin, overall survival, and liposomal verteporfin blood levels at timepoints following administration. Response will be determined per RANO criteria for MRI evaluation of GBM. Response rate will be estimated, and a 95% confidence interval will be estimated using the Clopper-Pearson method. Overall survival is defined as time from study enrollment to death or last follow-up, and will be estimated using the Kaplan-Meier method. Liposomal verteporfin blood levels are continuous measurements, which will be summarized descriptively using mean, median, standard deviation, and range at each time point.

11.3Interim analysis

An interim analysis for futility will be included as part of the Phase 2 portion of the study using Simon's two-stage approach. Please see Section 11.1 for more details.

12. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

12.1 Comprehensive Adverse Events and Potential Risks List

Adverse Event List for Visudyne (liposomal verteporfin))(from package insert)

The most frequently reported adverse reactions to VISUDYNE are injection site reactions (including pain, edema, inflammation, extravasation, rashes, hemorrhage and discoloration) and visual disturbances (including blurred vision, flashes of light, decreased visual acuity and visual field defects, including scotoma). These events occurred in approximately 10%-30% of patients. Of note nearly all patients reporting events were undergoing photodynamic therapy for various eye diseases,

The following events, listed by Body System, were reported more frequently with VISUDYNE therapy than with placebo therapy and occurred in 1%-10% of patients:
Ocular Treatment Site: Blepharitis, cataracts, conjunctivitis/conjunctival infection, dry eyes, ocular itching, severe vision decrease with or without subretinal/retinal or vitreous hemorrhage

Body as a Whole: Asthenia, fever, flu syndrome, infusion related pain primarily presenting as back pain, photosensitivity reactions

Cardiovascular: Atrial fibrillation, hypertension, peripheral vascular disorder, varicose veins
Dermatologic: Eczema
Digestive: Constipation, gastrointestinal cancers, nausea
Hemic and Lymphatic: Anemia, white blood cell count decreased, white blood cell count increased
Hepatic: Elevated liver function tests
Metabolic/Nutritional: Albuminuria, creatinine increased
Musculoskeletal: Arthralgia, arthrosis, myasthenia
Nervous System: Hypesthesia, sleep disorder, vertigo
Respiratory: Cough, pharyngitis, pneumonia
Special Senses: Cataracts, decreased hearing, diplopia, lacrimation disorder
Urogenital: Prostatic disorder
Non-ocular Events: Chest pain and other musculoskeletal pain during infusion

12.2 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

12.3 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

12.4 Classification of an Adverse Event

12.4.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

12.4.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other

factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

12.5 Adverse Event and Serious Adverse Event Reporting

12.5.1 Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

12.5.2 Adverse Event Reporting

From the time of treatment allocation/randomization through **21** days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.
The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.
Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.
Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:
1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 12.3 and which seriousness criteria have been met.
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.
Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.
Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.
Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.
Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

12.5.3 Serious Adverse Event Reporting

For the time period beginning at treatment allocation/randomization through **21** days following cessation of treatment, or **21** days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, FDA or supporting Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.
All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.
An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.
Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.
Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

Reporting Requirements for IND holder
For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

All SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

MedWatch 3500 Reporting Guidelines:
Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.
A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

7 Calendar-Day Telephone or Fax Report
The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.
FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.
The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with IRB P &Ps, all applicable global laws and regulations.

12.5.4 Expedited reporting requirements for phase 1/2 studies under IND w/in 30 days of last administration of the investigational agent/intervention

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.

12.5.5 Second and secondary malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.**

Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.
A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

12.5.6 Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

13. DATA MANAGEMENT/ REGULATORY REQUIREMENTS

13.1 Data Reporting

Study staff are responsible for submitting data and/or data forms in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the Associate Director of Clinical Research or the Director of Clinical Trials may temporarily suspend enrollment. Data entry is to be completed within the designated timeframe, not to exceed 30 days of the subject visit.
Queries will be resolved by the research staff within the time frame specified by the protocol, not to exceed 2 weeks.

13.1.1 Source data and documents

In accord with section 1.51 of the ICH E6 document all information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.
Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

Protocol Adherence

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

Retention of Study Documents

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

13.2 Data and Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur

within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

14. ETHICS AND PROTECTION OF HUMAN SUBJECTS

14.1 Ethical standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, as well as the federal regulations pertaining to ICH E6.

14.2 Institutional review board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

14.3 Informed Consent Process

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

Informed consent is a process that is initiated prior to the individual consent to participate in the study and continues throughout the individual's participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Consent will be done in person or remotely through secured email, phone or by electronic consenting using one of the methods that is Emory LITS approved (e.g. DocuSign) when available. We will follow Emory's guidance on use of electronic informed consent.

14.3.1 Non-English Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician. A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception) *N/A* ☒

Participants who are not yet adults (infants, children, teenagers) *N/A* ☒

14.3.2 Cognitively Impaired Adults N/A x

14.3.3 Adults Unable to Consent N/A ☒

14.4 Process to Document Consent in Writing

Consent will be obtained in writing. Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

14.5 Setting

Study treatment will take place in the phase 1 unit at Emory University. Consent may be obtained there or in the neuro-oncology clinics of the investigators at Emory University Clifton Road campus or Emory Midtown.

14.6 Resources Available

Emory`s large referral base and multidisciplinary cancer clinic will enable us to enroll **1** patient every 2-3 months. Potential candidates will also be identified in multidisciplinary tumor boards.

14.7 Provision to Protect the Privacy Interests of Participants

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No

information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

14.8 Economic Burden to Participants

Study drugs used in this study will be free of charge to the participants. Any costs associated with the research procedures will be paid for by the study and no cost to the patient. The study will not pay for patient`s regular medical care and standard of care studies, procedures, examinations.

14.9 Research use of stored samples, specimens, or data

Samples and data collected under this protocol may be used to study **glioblastoma.** Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

14.10 Multi-Site Research when Emory is the Lead Site*N/A ☒

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance 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.

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APPENDIX B ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin

Abbreviation or special term	Explanation
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IL	Interleukin
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PK	Pharmacokinetic(s)
PR	Partial response
qw	Every week
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1

Abbreviation or special term	Explanation
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SoC	Standard of Care
ULN	Upper limit of normal