Title:	Standard Chemotherapy versus Chemotherapy Chosen by **C**ancer **S**tem **C**ell Chemosensitivity Testing in the Management of Patients with **R**ecurrent Glioblastoma Multiforme (**GBM**) and recurrent WHO Grade III Glioma
Type of Clinical Trial	Pivotal Randomized Clinical Trial
Drug or Device Name(s):	ChemoID Drug Response Assay
FDA IND or IDE	N/A
Sponsor:	Cordgenics, LLC
IRB Protocol	20172720
Approval Date:	01/04/2018
ClinicalTrials.gov	NCT03632135

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ABBREVIATIONS AND DEFINITIONS OF TERMS

°C	Degrees centigrade
AE	Adverse event
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CSM	Centers for Medicare & Medicaid Services
DCC	Data Coordinating Center
DICOM	Digital Imaging and Communications in Medicine
DRE	Disease-Related Event
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board

ISM	Independent Safety Monitor
LDT	Laboratory Developed Test
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RANO	Response Assessment in Neuro-Oncology Criteria
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

ABSTRACT

Context: (Background)

The purpose of this clinical study is to confirm the utility of chemosensitivity tumor testing on cancer stem cells (ChemoID) as a predictor of clinical response in poor prognosis malignant brain tumors such as recurrent glioblastoma (GBM) and recurrent WHO III Glioma. At recurrence, a minority of patients is eligible for second surgery or re-irradiation, based on appropriate patient selection.

For the chemotherapy portion of their treatment, the management of recurrent glioblastoma and WHO III Glioma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease. Recurrent or progressive glioblastoma and recurrent WHO III Glioma are most commonly treated with nitrosoureas, temozolomide, CPT-11, bevacizumab, and/or combinations of these agents.

Patients with recurrent GBM and recurrent WHO III Glioma will receive standard therapy consisting of surgical resection and/or biopsy as dictated by whether or not they are resectable and for the chemotherapy portion of their treatment participants will be ***randomized*** between treatments chosen by the physician (standard of care) or medications selected by the chemo-sensitivity drug assay.

The idea is similar to when we test for bacterial sensitivity against antibiotics in case of a bacterial infection. The ChemoID test utilizes sample specimens obtained following standard of care indicated surgical resection and/or biopsy for the treatment of brain cancer.

Objectives: (primary and important secondary objectives)

The primary objective of this study is to compare patients with recurrent GBM and WHO grade III gliomas receiving standard of care versus chemosensitivity assay-guided chemotherapy for the chemotherapy portion of their therapy:

- Median Overall Survival (OS).

The secondary objectives of this study are to compare:

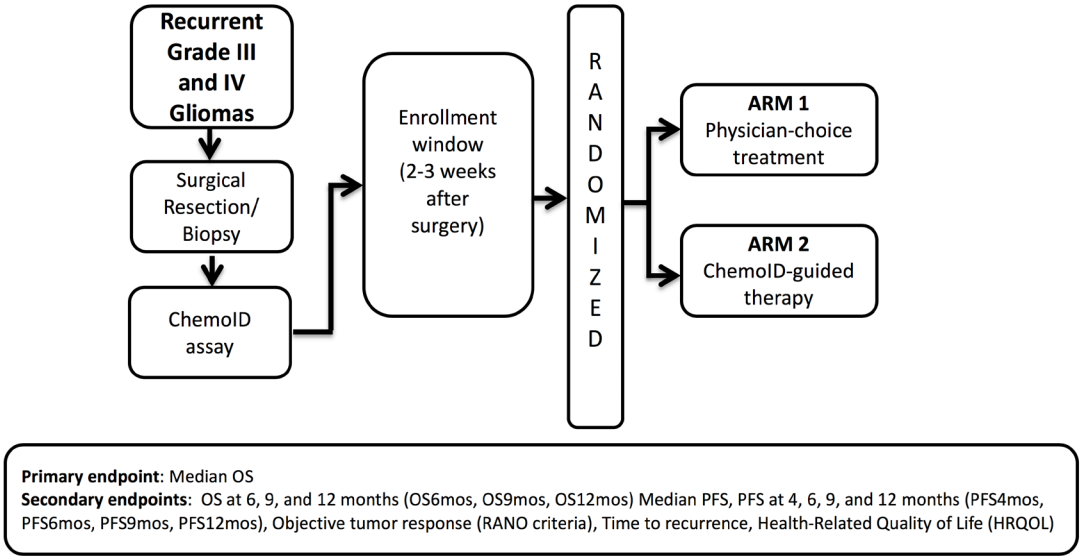
- Overall Survival at 6, 9 and 12 months (OS_{6mo}, OS_{9mo}, OS_{12mo})
- Median Progression Free Survival (PFS)
- Progression Free Survival at 4, 6, 9, and 12 months (PFS_{4mo}, PFS_{6mo}, PFS_{9mo}, PFS_{12mo})
- Objective tumor response measured by RANO (Response Assessment in Neuro-Oncology Criteria)
- Time to recurrence
- Health-Related Quality of Life (HRQOL)

Study Design:

Basic design: Parallel Group Randomized Controlled Clinical Trial.

Eligible patients with recurrent resectable GBM (who undergo surgical resection or a biopsy) and recurrent WHO grade III glioma will be consented to the trial. Specimens will be evaluated for cancer stem cell chemosensitivity testing (ChemoID).

Participants will be registered to the trial and ***randomized*** to either (**ARM 1**) standard of care chemotherapy chosen by physician, or (**ARM 2**) ChemoID-guided therapy as depicted in the schema below:



Setting/Participants:

The primary settings for this study are:

1. Allegheny Health Network, Pittsburgh, PA
2. University of Mississippi Medical Center, Jackson, MS
3. Univ. of Cincinnati Brain Tumor Center, Cincinnati, OH
4. Penn State Hershey Neuroscience Institute, Hershey, PA
5. The University of Toledo, Eleanor N. Dana Cancer Center, Toledo, OH
6. Charleston Area Medical Center, Charleston, WV
7. Maine Medical Center Research Institute, Scarborough, ME
8. Providence Brain and Spine Institute, Portland, OR
9. Thomas Jefferson University Hospital, Philadelphia, PA
10. St. Luke's University Health Network, Bethlehem, PA

11. Louisiana State University Health Sciences Center, New Orleans, LA
12. Kaiser Permanente, Los Angeles, CA
13. University of Southern California, Los Angeles, CA

Study Interventions and Measures:

Primary study outcome measure: To evaluate median overall survival (OS) in recurrent GBM patients who have had a ChemoID assay-guided treatment compared to standard therapy chosen by the physician.

Secondary outcome measures: Evaluate if recurrent GBM patients treated with drugs predicted by the ChemoID drug response assay will have better additional outcomes as compared to patients treated with standard of care drugs by measuring:

- Overall Survival at 6, 9 and 12 months (OS_{6mo}, OS_{9mo}, OS_{12mo})
- Median Progression Free Survival (PFS)
- Progression Free Survival at 4, 6, 9, and 12 months (PFS_{4mo}, PFS_{6mo}, PFS_{9mo}, PFS_{12mo})
- Objective tumor response measured by RANO (Response Assessment in Neuro-Oncology Criteria)
- Time to recurrence
- Better Health-Related Quality of Life (HRQOL) as an outcome measure to ChemoID treatment selection using self-reported, and validated questionnaires, addressing physical, psychological, emotional, and social issues.

PROTOCOL SYNOPSIS

Standard treatment with temozolomide and radiotherapy for patients with newly diagnosed glioblastoma has increased the median overall survival and, more importantly, the 2-year survival rate of patients. However, as yet, no investigations have been conducted to define effective strategies against recurrence, which occurs in most patients following combined radiotherapy/temozolomide treatment. As a consequence, recurrent glioblastoma (GBM) WHO Grade IV patients have a poor prognosis.

At recurrence, a minority of patients is eligible for second surgery or re-irradiation, based on appropriate patient selection. For the chemotherapy portion of their treatment, the management of recurrent glioblastoma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease. Recurrent or progressive glioblastoma is most commonly treated with nitrosoureas, temozolomide, CPT-11, bevacizumab, and/or combinations of these agents.

The drug sensitivity assay ChemoID is a CLIA certified and CAP accredited clinical laboratory functional test that uses patient's live tumor cells to indicate which chemotherapy agent (or combinations) will kill not only cancer cells, but also more importantly the cancer stem cells (CSCs) that are known to cause cancer to recur. Targeting of CSCs alongside the bulk of other cancer cells is a new paradigm in cancer treatment.

Upon obtaining informed consent, participants with recurrent GBM who can be surgically resected will be registered to the trial and have tumor biopsy samples undergo CSCs chemosensitivity testing with multiple FDA approved chemotherapeutic agents.

Participants will be ***randomized*** to either:

(**ARM 1**) standard of care chemotherapy chosen by the physician

or

(**ARM 2**) ChemoID-guided therapy.

Participants will be assessed by either brain MRI with contrast or CT scan with contrast at 2-3 month intervals after therapies as per standard-of care.

Results of clinical response to standard of care therapy or to ChemoID guided chemotherapy agents will be used to determine the predictive value of chemosensitivity testing in recurrent GBM patients as follows:

Primary endpoint: Median overall survival (OS).

Secondary endpoints: Overall Survival at 6, 9, and 12 months (OS_{6mo}, OS_{9mo}, OS_{12mo}), Median Progression Free Survival (PFS), Progression Free Survival at 4, 6, 9, and 12 months (PFS_{4mo}, PFS_{6mo}, PFS_{9mo}, PFS_{12mo}), Objective tumor response measured by RANO (Response Assessment in Neuro-Oncology Criteria), Time to recurrence. Other outcomes measured will be Health-Related Quality of Life (HRQOL) as an outcome measure using a self-reported, and validated questionnaire, addressing physical, psychological, emotional, and social issues.

Procedures to be performed:

This clinical study utilizes sample specimens obtained during:

1. The routine surgical resection of already diagnosed recurrent cancer

Standard biopsy procedures or resection of tumors will be conducted by the surgeons who routinely perform these procedures. The current study will utilize only sample specimens obtained by established procedures that patients have to routinely undergo for the treatment of his/her recurrent cancer; there is no additional risk to the patient. Tissue for this study will only be obtained when it is assured that there is adequate tissue for routine histologic analysis. At no time will tissue be obtained solely for the purpose of carrying out the chemo-sensitivity assay.

After its removal, the biopsy or surgical specimen will be placed in a container with transportation medium. The container will be labeled and then shipped to the ChemoID laboratory at the Translational Genomics Research Institute (TGRI) in Cabell Huntington Hospital. ChemoID assay is performed by well-trained medical technologists in a Clinical Laboratory Improvement Amendments (CLIA) certified facility under the Centers for Medicare & Medicaid Services (CMS) guidelines. The performance characteristics of the ChemoID assay in terms of its accuracy, precision, analytical sensitivity and analytical specificity are certified by both CLIA and College of American Pathologists (CAP). The clinical utility of the assay as performed is documented in several peer-reviewed publications and ASCO abstracts (1-7).

Study Title	**Standard chemotherapy versus chemotherapy chosen by cancer stem cell chemosensitivity testing in the management of patients with recurrent Glioblastoma Multiforme (GBM)** and recurrent WHO Grade III Glioma**.**
Funder	ChemoID
Clinical Phase	III
Study Rationale	At recurrence, a minority of patients is eligible for second surgery or re-irradiation, based on appropriate patient selection. There is no standard of care for the chemotherapy portion of their treatment, and the management of recurrent glioblastoma and recurrent WHO III Glioma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease. Recurrent or progressive glioblastoma is most commonly treated with nitrosoureas, temozolomide, CPT-11, bevacizumab, and/or combinations of these agents. The ability to individualize therapy by providing the treating physician with drug response information on a panel of approved drugs should aid in the selection of effective therapy for individual patients, thus resulting in improved outcomes. ChemoID assay is a high-complex CLIA and CAP certified chemosensitivity test that uses a patient's live tumor cells to indicate which chemotherapy agent (or "combinations") will kill not only the bulk of the cancer tumor but also the cancer stem cells (CSCs). Because CSCs are very resistant to chemotherapy and radiation, empirical choice treatments often fail to choose drugs that act on CSCs, which are responsible for tumor recurrence. Targeting of CSCs alongside the bulk of other cancer cells is a new paradigm in cancer treatment. This constitutes an important advantage of ChemoID approach in the management of newly diagnosed glioma patients. We would like to determine the clinical validity of chemosensitivity tumor testing on the bulk tumor cells as well as cancer stem cells as a predictor of clinical response in the management of recurrent glioblastoma.
Study Objective(s)	The primary objective of this study is to compare patients with recurrent GBM and recurrent WHO grade III glioma receiving standard of care versus chemosensitivity assay-guided chemotherapy for the chemotherapy portion of their therapy: Median Overall Survival (OS).

	The secondary objectives of this study are to compare: • Overall Survival at 6, 9, and 12 months (OS_{6mo}, OS_{9mo}, OS_{12mo}) • Median Progression Free Survival (PFS) • Progression Free Survival at 4, 6, 9, and 12 months (PFS_{4mo}, PFS_{6mo}, PFS_{9mo}, PFS_{12mo}) • Objective tumor response measured by RANO (Response Assessment in Neuro-Oncology Criteria) • Time to recurrence • Health-Related Quality of Life (HRQOL)
Test Article(s) *(If Applicable)*	ChemoID assay is a high-complex CLIA and CAP certified drug response assay that uses a patient's live tumor cells to indicate which chemotherapy agent (or "combinations") will kill not only the bulk of the cancer tumor but also the cancer stem cells (CSCs). CSCs are a small sub-population of cancer cells within a patient's tumor that are very resistant to chemotherapy and radiation and that are responsible of cancer recurrence. Empirical choice treatments often fail to choose drugs that act on CSCs. This may help to explain why early tumor shrinkage is often poorly predictive of overall survival. While conventional therapies kill the bulk of non-stem cancer cells, resulting in tumor shrinkage, CSCs may remain viable and later reestablish the tumor, leading to relapse. A potential new approach to address this is the targeting of both CSCs and bulk tumor cells with most effective chemotherapy choices for improved clinical outcome. ChemoID assay serves as a clinically actionable tool for oncologists by measuring percent of cell kill of CSCs and bulk tumor cells by direct visualization and quantification of cell death following exposure to FDA approved chemotherapy agents. When ordering the assay, a physician selects each of the multiple treatments under consideration for a given patient for inclusion in the assay.
Study Design	The proposed study is a parallel group randomized controlled clinical trial. Upon obtaining informed consent, participants with recurrent GBM who can be surgically resected will be registered to the trial and have tumor biopsy samples undergo CSCs chemosensitivity testing with multiple FDA approved chemotherapeutic agents. Then participants will be ***randomized*** to either: (**ARM 1**) Standard of care chemotherapy chosen by the physician or

	(**ARM 2**) ChemoID-guided therapy.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Men and Women and members of all ethnic groups who are at least 18 years old at the time of enrollment are eligible for this trial; 2. Informed consent obtained and signed; Informed consent obtained and signed; Informed consent may be obtained from a legal authorized representative when the person is not competent, incapacitated, or otherwise unable to make an informed judgment 3. Willing and able to commit to study procedures including long-term follow-up visit(s) on or off the study protocol; 4. Histopathologically confirmed 2016 WHO grade III recurrent glioma, and grade IV recurrent glioblastoma (GBM), inclusive of Gliosarcoma. 5. In all cases, the diagnosis must be confirmed by a pathologist. 6. Recurrent surgically resectable tumor and/or biopsy; 7. Participants who have undergone surgical resection should have received an MRI or a scan after surgery in order to visualize residual tumor. If not, the operative report must be available; 8. Prior to surgery there was imaging evidence of measurable progressive disease (PD); 9. Re-radiation, if indicated, should occur at least 2 weeks after surgery and/or biopsy once the wound has healed well without any drainage or cellulitis; 10. Estimated survival of at least 3 months; 11. Hgb > 9 gm; absolute neutrophil count (ANC) > 1500/µl; platelets > 100,000; Creatinine < 1.5 times the upper limit of laboratory normal value; Bilirubin < 2 times the upper limit of laboratory normal value with the exception of Gilbert's syndrome; serum glutamate pyruvate transaminase (SGPT) or serum glutamate oxaloacetate transaminase (SGOT) < 3 times the upper limit of laboratory normal value; 12. Chemotherapy must start within 8 weeks of tumor resection or biopsy; 13. Bevacizumab (Avastin) is allowed. If indicated it should be initiated at least 4 weeks post craniotomy or biopsy if the wound has healed well without any drainage or cellulitis; 14. The use of herbal preparation or

tetrahydrocannabinol/cannabidiol is strongly discouraged, but not contraindicated;

Exclusion Criteria

1. Subjects with newly diagnosed GBM
2. Pregnant women or nursing mothers cannot participate in the study. Women of childbearing age must have a negative pregnancy test prior to study entry. Women of childbearing potential must practice medically approved contraceptive precautions;
3. Abnormal hematological results at inclusion with:
   - Neutrophils < 1,500/mm3
   - Blood-platelets < 100,000/mm3
4. Severe or chronic renal insufficiency (creatinine clearance ≤ 30 ml/min);
5. Patient unable to follow procedures, visits, examinations described in the study;
6. Any usual formal indication against imaging examinations (important claustrophobia, pacemaker);
7. History of another malignancy in the previous 2 years, with a disease-free interval of < 2 years. Patients with prior history of in situ cancer or basal or squamous cell skin cancer, any time prior to screening, are eligible.
8. OPTUNE device is not permitted in the study;
9. Patients cannot participate to any clinical trials utilizing a liquid biomarker or imaging studies that impact the overall survival.

Number Of Subjects	Total Number of Subjects (150, or until the primary endpoint is met) Total Number of Sites (13)
Study Duration	Each subject's participation will last up to 3 years The entire study is expected to last 3-5 years
Study Phases	3 phases
1- Screening	1) Screening for eligibility and obtaining consent
2- Study Treatment	2) Resection or biopsy of tumor and *Randomization* study of Standard-of-Care chemotherapy vs. ChemoID-guided treatment in recurrent GBM patients 3) Study visits with clinical assessment and brain MRI or CT scan

3- Follow-Up	with contrast. Clinical lab, visit, and MRI or CT imaging as per standard of care. HRQoL.
Efficacy Evaluations	Primary outcome: Median Overall Survival (OS). Secondary outcomes: Overall Survival at 6, 9, and 12 months (OS_{6mo}, OS_{9mo}, OS_{12mo}), Median Progression Free Survival (PFS), Progression Free Survival at 4, 6, 9, and 12 months (PFS_{4mo}, PFS_{6mo}, PFS_{9mo}, PFS_{12mo}), objective tumor response measured by RANO (Response Assessment in Neuro-Oncology Criteria) (8) on brain MRI or CT scans with contrast), time to recurrence, and Health-Related Quality of Life.
Pharmacokinetic Evaluations	(N/A)
Safety Evaluations	Chemotherapies used are FDA approved to treat this disease and are part of standard of care
All Statistical And Analytic Plan	The primary endpoint of improved median overall survival will be examined using logistic regression under an intention to treat analysis.
DATA AND SAFETY MONITORING PLAN	A DSMB will be responsible to monitor data quality management and ongoing assessment of safety

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Treatment/ Intervention**				**Follow-up visits**												
Visit Number		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-24**
Informed Consent/Assent	X																	
Review Inclusion/Exclusion Criteria	X																	
Demographics/Medical History	X																	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs: BP, HR, RR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight	X																	
Pregnancy Test	X																	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Evaluation (if collected as per standard of care)	X	X			X	X		X		X		X		X		X		(13, 15, 17, 19, 21, 23) X
Brain MRI or CT scan with or w/o contrast (if collected as per standard of care)	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessment	X					X	X	X	X	X	X	X	X	X	X	X	X	X
HRQOL assessment					X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Phase (contd.)	**Screening**	**Treatment/ Intervention**				**Follow-up visits**												
Visit Number (contd.)		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-24**
Scheduling for Surgical removal and Tumor Biopsy for Diagnosis, and ChemoID testing (at the same time)		X																
Randomization of patients to receive either physician choice chemotherapy or ChemoID-guided therapy			X															
Review of Pathology report (MGMT, IDH-1)			X															
Review of ChemoID drug response assay for Arm 2 participants					X													
Dispense Chemotherapy Drug as per assigned ARM					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Compliance					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment					X	X	X	X	X	X	X	X	X	X	X	X	X	X

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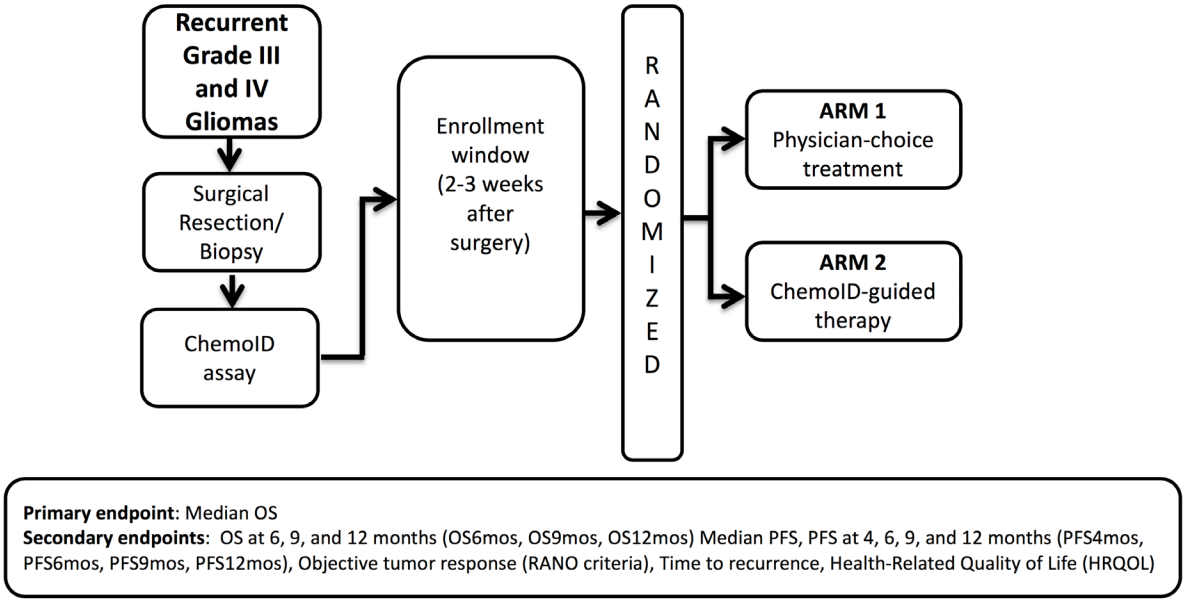
STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

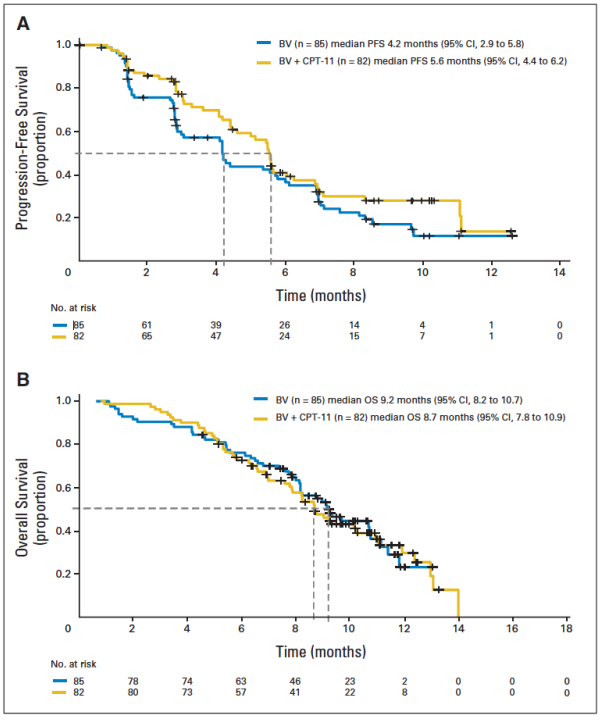
1.1 Introduction

Recurrent glioblastoma WHO Grade IV patients have poor prognosis.

At recurrence, only a fraction of patients is eligible for second surgery or reirradiation, based on appropriate patient selection. Additionally, for the chemotherapy portion of their treatment, there is no consensus on the management of recurrent glioblastoma as new therapeutic principles enrich the standards of care for newly diagnosed disease.

Although, no investigations have been conducted to define effective strategies against recurrence that occurs in most patients following combined radiotherapy/temozolomide regimens, treatment of recurrent or progressive glioblastoma with nitrosoureas, temozolomide, CPT-11, bevacizumab, and/or combinations of these agents are most commonly used.

Following is a Kaplan-Meier plot of survival curve comparing progression free survival (Panel A) and overall survival (Panel B) of GBM recurrent patients treated with Bevacizumab (BV) alone or with Bevacizumab + CPT11 (BV+CPT11) demonstrating that the median PFS times were 4.2 months (95.0% CI, 2.9 to 5.8 months) for the BV group and 5.6 months (95.0% CI, 4.4 to 6.2 months) for the BV + CPT-11 group (Panel A), and that the median OS times from the time of random assignment were 9.2 months (95.0% CI, 8.2 to 10.7 months) for the BV group and 8.7 months (95.0% CI, 7.8 to 10.9 months) for the BV + CPT-11 group (Panel B) (9).



From: Friedman H.S. et al. Bevacizumab Alone and in Combination With Irinotecan in Recurrent Glioblastoma. J. Clin Oncol 27:4733-4740, 2009.

The ChemoID drug response assay is a CLIA certified and CAP accredited functional test that uses patient's live tumor cells to indicate which chemotherapy agent (or combinations) will kill not only cancer cells, but more importantly the cancer stem cells (CSCs) that are known to cause cancer to recur.

The **rationale** for this study is that current treatments often fail to choose drugs that act on CSCs, which are responsible for therapy resistance and cancer progression. Recurrent glioblastoma remains a largely unmet medical need, which highlights the need for effective therapies. Targeting of CSCs alongside the bulk of other cancer cells is a new paradigm in cancer treatment. This constitutes an important advantage of ChemoID approach over other assays available. By testing multiple chemotherapies on a patient's tumor cells before clinically treating a cancer patient, ChemoID drug response assay may enable faster reaction time to administer the optimum selection of chemotherapy drug(s), increased patient survival, and lower treatment costs by eliminating unnecessary chemotherapies, and decreased levels of toxicity.

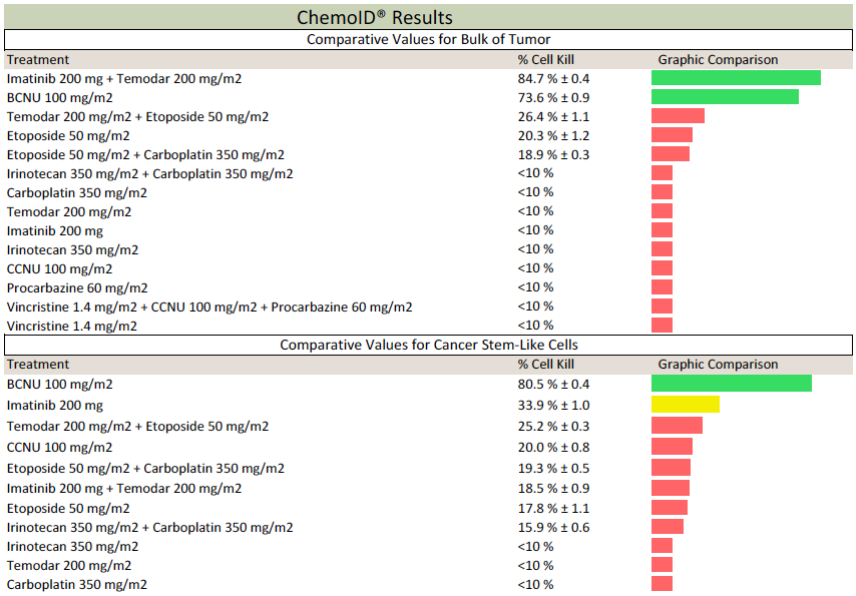
ChemoID drug response assay in a clinical study of 42 consecutively treated patients showed statistically significant improved response rate (2.2-fold increase) in patients who were given assay-indicated chemotherapy. Results from this study indicate that a drug response assay that targets CSCs may be a very useful tool for optimizing treatment selection when first-line therapy fails and when there are multiple clinically acceptable and equivalent treatments available.

Additionally, the assay has been prospectively used in 30 additional GBM patients showing proof of assay-directed therapy to effectively determine chemotherapy regimens that improved clinical outcomes.

1.2 Name and Description of Investigational Product or Intervention

ChemoID is a functional drug response assay performed in a clinical laboratory at Cabell Huntington Hospital. The performance characteristics of the ChemoID assay in terms of its accuracy, precision, analytical sensitivity and analytical specificity are certified by CLIA (Clinical Laboratory Improvement Amendments) and CAP (College of American Pathologists). The test is performed under the Medicare & Medicaid Services (CMS) guidelines as a Laboratory Developed Test (LDT). The assay uses patient's live tumor cells to indicate which chemotherapy agent (or combinations) will kill not only cancer cells, but also and more importantly, the cancer stem cells (CSCs) that are known to cause cancer to recur.

Sample of a ChemoID Assay Report from a GBM patient



ChemoID® Results

Comparative Values for Bulk of Tumor

Treatment	% Cell Kill	Graphic Comparison
Imatinib 200 mg + Temodar 200 mg/m2	84.7 % ± 0.4	
BCNU 100 mg/m2	73.6 % ± 0.9	
Temodar 200 mg/m2 + Etoposide 50 mg/m2	26.4 % ± 1.1	
Etoposide 50 mg/m2	20.3 % ± 1.2	
Etoposide 50 mg/m2 + Carboplatin 350 mg/m2	18.9 % ± 0.3	
Irinotecan 350 mg/m2 + Carboplatin 350 mg/m2	<10 %	
Carboplatin 350 mg/m2	<10 %	
Temodar 200 mg/m2	<10 %	
Imatinib 200 mg	<10 %	
Irinotecan 350 mg/m2	<10 %	
CCNU 100 mg/m2	<10 %	
Procarbazine 60 mg/m2	<10 %	
Vincristine 1.4 mg/m2 + CCNU 100 mg/m2 + Procarbazine 60 mg/m2	<10 %	
Vincristine 1.4 mg/m2	<10 %	

Comparative Values for Cancer Stem-Like Cells

Treatment	% Cell Kill	Graphic Comparison
BCNU 100 mg/m2	80.5 % ± 0.4	
Imatinib 200 mg	33.9 % ± 1.0	
Temodar 200 mg/m2 + Etoposide 50 mg/m2	25.2 % ± 0.3	
CCNU 100 mg/m2	20.0 % ± 0.8	
Etoposide 50 mg/m2 + Carboplatin 350 mg/m2	19.3 % ± 0.5	
Imatinib 200 mg + Temodar 200 mg/m2	18.5 % ± 0.9	
Etoposide 50 mg/m2	17.8 % ± 1.1	
Irinotecan 350 mg/m2 + Carboplatin 350 mg/m2	15.9 % ± 0.6	
Irinotecan 350 mg/m2	<10 %	
Temodar 200 mg/m2	<10 %	
Carboplatin 350 mg/m2	<10 %	

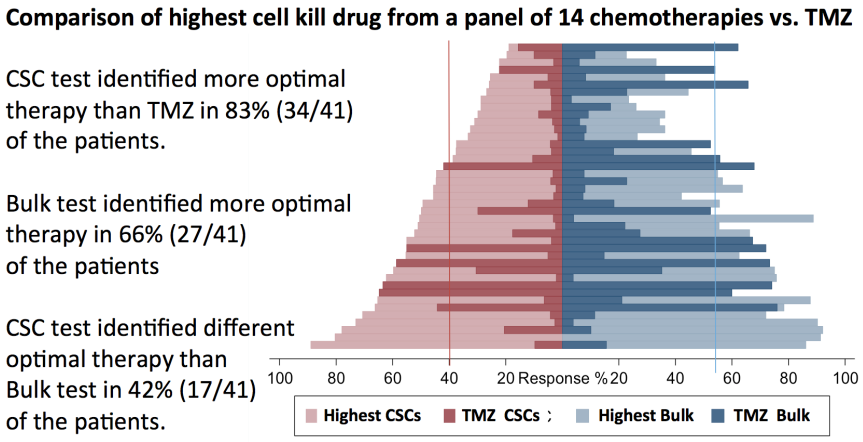
1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Clinical Studies

A prospective clinical investigation was conducted using the ChemoID assay to measure the sensitivity and resistance of CSCs and bulk of tumor cells cultured from 42 GBM clinical samples challenged with several chemotherapy agents, which were correlated to the clinical response of the treated patients, independently of other biomarkers. Patients were all treated with standard-of-care TMZ plus radiation with or without maximal surgery, depending on the status of the disease. Patients were prospectively monitored for tumor response, time to recurrence, progression-free survival (PFS), and overall survival (OS). Odds ratio (OR) associations of 12-month recurrence, PFS, and OS outcomes were estimated for CSC, bulk tumor, and combined assay responses for the standard-of-care TMZ treatment; sensitivities/specificities, areas under the curve (AUCs), and risk reclassification components were examined (6, 7).

Clinical Study Results: Median follow-up was 8 months (range 3-49 months). For every 5% increase in *in vitro* CSC cell kill by TMZ, 12-month patient response (non-recurrence of cancer) increased two-fold, OR = 2.2 (P = .016). Similar but somewhat less supported associations with the bulk tumor test were seen, OR = 2.75 (P = .07) for each 5% bulk tumor cell kill by TMZ. Combining CSC and bulk tumor assay results in a single model yielded a statistically supported CSC association, OR = 2.36 (P = .036), but a much attenuated remaining bulk tumor association, OR = 1.46 (P = .472). AUCs and [sensitivity/specificity] at optimal outpoints (N40% CSC cell kill and N55% bulk tumor cell kill) were AUC = 0.989 [sensitivity = 100/specificity = 97], 0.972 [100/89], and 0.989 [100/97] for the CSC only, bulk tumor only, and combined models, respectively. Risk categorization of patients was improved by 11% when using the CSC test in conjunction with the bulk test (risk reclassification nonevent net reclassification improvement [NRI] and overall NRI = 0.111, P = .030). Median recurrence time was 20 months for patients with a positive (N40% cell kill) CSC test versus only 3 months for those with a negative CSC test, whereas median recurrence time was 13 months versus 4 months for patients with a positive (N55% cell kill) bulk test versus negative. Similar favorable results for the CSC test were observed for PFS and OS outcomes.

Comparison of most sensitive drug from a panel of various chemotherapies vs. Temodar



Results across a panel of 14 potential other treatments indicated that 34/41 (83%) potentially more optimal alternative therapies may have been chosen using CSC results, whereas 27/41 (66%) alternative therapies may have been chosen using bulk tumor results.

A pyramid plot of percent cell kill for the most cytotoxic drug and TMZ comparing CSC and bulk tests for each patient is illustrated above. Optimal therapies with the highest cell kill are shown in light colors and TMZ cell kill is shown in dark colors with each row of the pyramid corresponding to results for a single patient. When the light bar is longer than the dark bar, a potentially more optimal therapy than TMZ is identified. CSC results outlined in red show patients whose CSC test identified an optimal therapy that was different than the optimal therapy identified by the bulk test, 17/41 patients, 42% (95%CI 26-57%) p<0.001.

1.4 Selection of Drugs and Dosages

List of Current Chemotherapeutic Agents and suggested Combinations on the ChemoID® GBM Drug Panel

	Single Drug	Dose
1	Carboplatin	350 mg/m2 or 4 AUC
2	Irinotecan	125 mg/m2
3	Etoposide	50 mg/m2
4	BCNU	100 mg/m2
5	CCNU	100 mg/m2
6	Temozolomide	150-200 mg/m2
7	Procarbazine	60 mg/m2
8	Vincristine	1.4 mg/m2
9	Imatinib	400 mg
	Drug Combination	**Dose**
1	Procarbazine CCNU Vincristine	60 mg/m2 100 mg/m2 1.4 mg/m2
2	Carboplatin Irinotecan	350 mg/m2 or 4 AUC 125 mg/m2
3	Carboplatin Etoposide	350 mg/m2 or 4 AUC 50 mg/m2
4	Temozolomide Etoposide	50 mg/m2 50 mg/m2
5	Temozolomide Imatinib	50 mg/m2 200 mg

Patients should receive treatment per standard practice and may continue on treatment until progression per investigator discretion if having continued response and/or clinical benefit. The number of cycles of therapy should be administered as clinically appropriate, although it is suggested that patients should receive at least 4 cycles of therapy.

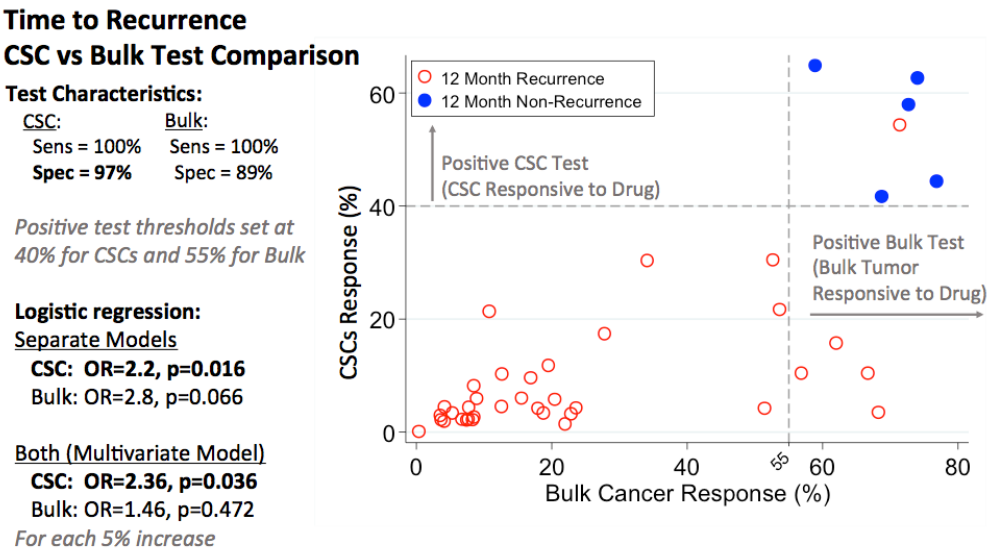
1.5 Relevant Literature and Data

The following figure illustrates the relationship between the TMZ CSC assay results

(%-cell kill on the y -axis) and TMZ bulk tumor assay results (%-cell kill on the x -axis) characterized by 12-month recurrence outcomes, with solid circles representing treatment responders (patients who did not manifest a recurrence at 12 months) and open circles representing patients manifesting recurrence within 12 months from treatment (6, 7). Referent lines are drawn at the optimal thresholds from the logistic regression models (40% for CSC, 55% for bulk tumor). In the upper-right quadrant are patients with high TMZ cell kill for both CSC and bulk tumor assays where 5/41 (12%) had prolonged tumor response and only 1 (2.4%) was recurrent. In the lower-left quadrant are patients with low TMZ cell kill for both CSC and bulk tumor assays; all 31 (76%) recurred within 12 months from treatment. Finally, the lower-right quadrant shows patients whose TMZ bulk tumor assay showed a high cell kill (> 55%) but whose TMZ CSC assay showed a low cell kill (< 40%); all 4/41 (10%) recurred within 12 months.

When the CSC assay results were considered separately, every 5% increase in TMZ CSC %-cell kill was associated with a significant two-fold increase in 12-month patient response (non recurrence of cancer), OR = 2.2 (95% CI 1.16-4.17), P = .016. TMZ bulk tumor %-cell kill was similarly associated but with less statistical support, OR = 2.8 (0.93-8.06) P = .066 for each 5% increase.

When the CSC and bulk test results were analyzed together in a single, multivariate model, the CSC test again showed a statistically supported OR of 2.36 (1.06-5.25) P = .036, whereas the bulk of tumor test association fell to OR = 1.46 (0.52-4.08) P = .472.

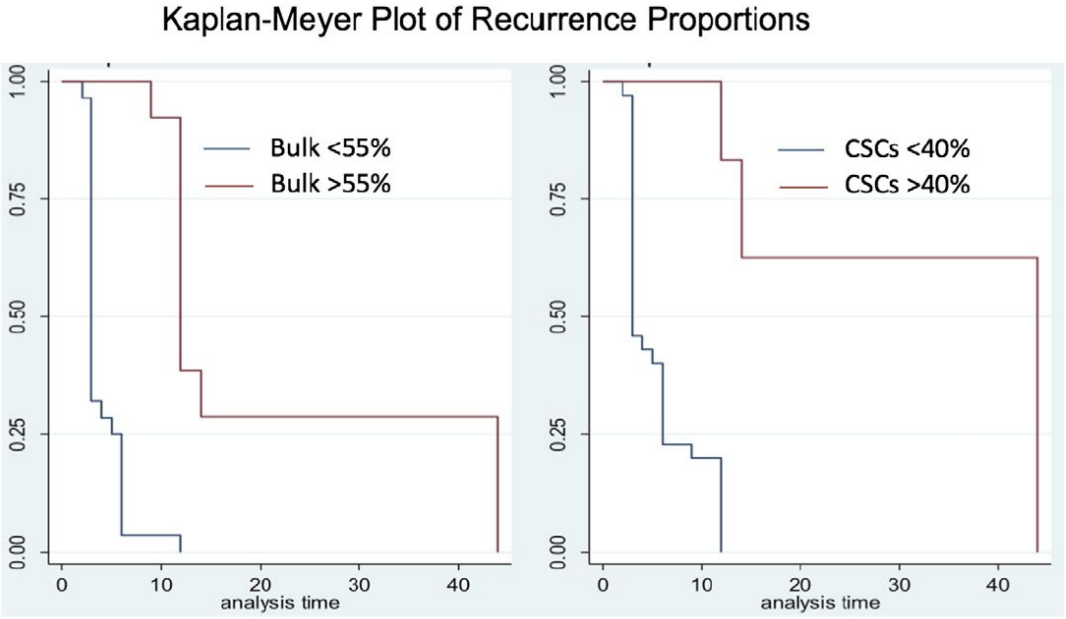


Quadrant diagram of the relationship between TMZ CSC assay results (%-cell kill on the y-axis) and TMZ bulk tumor assay results (%-cell kill on the x-axis) characterized by 12-month recurrence outcomes. Solid circles represent treatment responders (patients who did not manifest a recurrence at 12 months), and open circles represent patients manifesting recurrence within 12 months from treatment. Optimal threshold referent lines from the logistic regression models (40% for CSC, 55% for bulk tumor) are illustrated.

ChemoID assay areas under the curve were high for all three models:

AUC = 0.989, 0.972, and 0.989 for the separate CSC, bulk tumor, and combined model, respectively. Related optimal thresholds for the assays were 40% CSC cell kill and 55% bulk tumor cell kill by TMZ which then provided sensitivities/specificities of 100/97, 100/89, and 100/97 for the three models, respectively. Both the CSC assay and the bulk tumor assay performed well in these models and in related secondary models for OS & PFS, with the CSC assay showing slightly improved results over the bulk tumor results throughout.

The following figure shows Kaplan-Meyer plots of time to recurrence stratified by ChemoID test results from the clinical study using the optimal TMZ thresholds (40% cell kill for CSC and 55% cell kill for bulk tumor). Patients with positive ChemoID CSC tests (>40% cell kill) had longer median times to recurrence (20 months) than those with negative CSC tests (3 months). Patients with positive bulk tumor tests (>55% cell kill) had longer median times to recurrence (13 months) than those with negative bulk tumor tests (4 months), but the separation was not as great.



Kaplan-Meier plots of tumor recurrence across the study period. Survival (tumor non recurrence) is shown stratified by dichotomized test results (TMZ optimal thresholds of CSCs> 40% and bulk test >55%); *P* for both <.001 in Cox proportional hazard models.

1.6 Compliance Statement

This study will be conducted in full accordance of all applicable Research Policies and Procedures of the investigators institution and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with the ASRI-WPAHS IRB Policies IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine the validity of chemosensitivity (ChemoID) tumor testing on cancer stem cells as a predictor of clinical response in recurrent glioblastoma and recurrent WHO grade III glioma

2.1 Primary Objective (or Aim)

The primary objective of this study is to compare patients with recurrent GBM and recurrent WHO grade III glioma who receive the standard of care versus chemosensitivity assay directed chemotherapy for the chemotherapy portion of their therapy:

- Median Overall Survival (OS).

2.2 Secondary Objectives (or Aims)

The secondary objectives of this study are to compare:

- Overall Survival at 6, 9 and 12 months (OS_{6mo}, OS_{9mo}, OS_{12mo})
- Median Progression Free Survival (PFS)
- Progression Free Survival at 4, 6, 9, and 12 months (PFS_{4mo}, PFS_{6mo}, PFS_{9mo}, PFS_{12mo})
- Objective tumor response measured by RANO (Response Assessment in Neuro-Oncology Criteria)
- Time to recurrence
- Health-Related Quality of Life (HRQOL)

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This study is designed as a **parallel group randomized controlled clinical trial** to determine if recurrent GBM patients treated with drugs predicted by ChemoID assay will have better outcomes than patients treated with standard of care.

3.1.1 Screening Phase

Eligible patients with recurrent GBM and recurrent 2016 WHO grade III glioma will be identified using the protocol inclusion and exclusion criteria and will be consented to the trial.
Under standard-of-care, patients will be screened using brain MRI with gadolinium contrast, which will be followed by tumor resection and biopsy procedure.

3.1.2 Study Treatment Phase 1 (start of the study intervention)

Under standard-of-care, eligible participants will undergo surgical resection and/or biopsy.

Fresh tissue tumor biopsies will be sent to Pathology to confirm diagnosis of GBM or recurrent WHO grade III glioma, the methylation status of the MGMT gene promoter, and a portion of the fresh biopsy will be sent to the ChemoID lab at the Cabell Huntington Hospital, WV to perform the drug response assay.

Shipment of samples to the ChemoID lab are performed using a secure shipping container for biological samples and the FEDEX carrier using standardized procedure under CLIA and CAP regulations.

Participants with recurrent GBM will be registered to the trial.

Informed consent will be obtained prior to any study related procedures being performed, including discontinuation of current therapy.

An MRI (or CT if patient is unable to have an MRI performed) of the brain with and without contrast will have been performed within 14 days of the screening visit.

Blood samples will be drawn as per standard-of-care and will be used to confirm eligibility based on clinical laboratory parameters. Females will have a urine or serum pregnancy test.

3.1.3 Study Treatment Phase 2

All recurrent GBM and recurrent WHO grade III glioma participants registered to the trial will be ***randomized*** using a computer-generated process and placed in the appropriate study arm.

3.1.4 Study Treatment Phase 3

Participants will be treated according to the randomly assigned study arm:

(**ARM 1**) standard of care chemotherapy chosen by the physician

or

(**ARM 2**) ChemoID-guided therapy.

3.1.5 Follow-up Phase

Participants will be followed according to standard-of-care intervals by neurologic and neurosurgical clinical assessments preferably with brain MRI scans pre- and post intravenous gadolinium contrast unless the patient has a contraindication to gadolinium contrast then non-contrast brain MRI will be obtained and or CT-scans of the brain pre and post intravenous contrast or without contrast if the patient has a contraindication to CT IV contrast such as severe allergy and/or renal dysfunction.

Response to chemotherapy will be evaluated according to the 2D Response Assessment in Neuro-Oncology (RANO) criteria, in which in addition to contrast enhancement, tumor extension on T2- and fluid-attenuated inversion recovery (FLAIR)-weighted MRI are evaluated (8). Furthermore, an assessment of neurological function and corticosteroid use is included.

The follow-up phase will continue for up to 3 years or death. At 6 and 12 months after Visit 24 there will be a phone call to assess survival status.

3.2 Allocation to Treatment Groups and Blinding

Participants will be randomized using a statistical random number generator in RedCap.

Participants will be treated according to the assigned study arm.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per subject will be up to 3 years or until death, with up to 3 days screening, up to 1 day Phase 1, up to 1 day Phase 2, and 1 day Phase 3, and 26 days follow-up. Participants will be followed according to standard-of-care intervals by neurologic and neurosurgical clinical assessments as detailed in Table 1: schedule of study procedures. Patient will be followed for overall survival on or off the clinical trial.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The settings for this study are:

1. Allegheny Health Network, Pittsburgh, PA
2. University of Mississippi Medical Center, Jackson, MS
3. University of Cincinnati, Brain Tumor Center, Cincinnati, OH
4. Penn State Hershey Neuroscience Institute, Hershey, PA
5. The University of Toledo, Eleanor N. Dana Cancer Center, Toledo, OH
6. Charleston Area Medical Center, Charleston, WV
7. Maine Medical Center Institute, Scarborough, ME
8. Providence Brain and Spine Institute, Portland, OR
9. Thomas Jefferson University Hospital, Philadelphia, PA
10. St. Luke's University Health Network, Bethlehem, PA
11. Louisiana State University Health Sciences Center, New Orleans, LA
12. Kaiser Permanente, Los Angeles, CA
13. University of Southern California, Los Angeles, CA

The total number of evaluable subjects projected is N=150 (see statistical section below).

3.4 Study Population

3.4.1 Inclusion Criteria

1) Men and Women and members of all ethnic groups who are at least 18 years old at the time of enrollment are eligible for this trial;
2) Informed consent obtained and signed; Informed consent may be obtained from a legal authorized representative when the person is not competent, incapacitated, or otherwise unable to make an informed judgment.
3) Willing and able to commit to study procedures including long-term follow-up visit(s) on or off the study protocol;
4) Histopathologically confirmed 2016 WHO grade III recurrent glioma, and grade IV recurrent glioblastoma (GBM), inclusive of Gliosarcoma;
5) In all cases, the diagnosis must be confirmed by a pathologist.
6) Recurrent surgically resectable tumor and or biopsy;
7) Participants who have undergone surgical resection should have received an MRI or a scan after surgery in order to visualize residual tumor. If not, the operative report must be available;
8) Prior to surgery there was imaging evidence of measurable progressive disease (PD);
9) Re-radiation, if indicated, should occur at least 2 weeks after surgery and/or biopsy, once the wound has healed well without any drainage or cellulitis;
10) Estimated survival of at least 3 months;
11) Hgb > 9 gm; absolute neutrophil count (ANC) > 1500/ul; platelets > 100,000; Creatinine < 1.5 times the upper limit of laboratory normal value; Bilirubin < 2 times the upper limit of laboratory normal value with the exception of Gilbert's syndrome; serum glutamate pyruvate transaminase (SGPT) or serum glutamate oxaloacetate transaminase (SGOT) < 3 times the upper limit of laboratory normal value;
12) Chemotherapy must start within 8 weeks of tumor resection or biopsy;
13) Bevacizumab (Avastin) is allowed. If indicated, it should be initiated at least 4 weeks post craniotomy or biopsy if the wound has healed well without any drainage or cellulitis;
14) The use of herbal preparation or tetrahydrocannabinol/cannabidiol is strongly discouraged, but not contraindicated;

3.4.2 Exclusion Criteria

1) Subjects with newly diagnosed GBM
2) Pregnant women or nursing mothers cannot participate in the study. Women of childbearing age must have a negative pregnancy test prior to study entry. Women of childbearing potential must practice medically approved contraceptive precautions;
3) Abnormal hematological results at inclusion with:

   a. Neutrophils < 1,500/mm3
   b. Blood-platelets < 100,000/mm3
4) Severe or chronic renal insufficiency (creatinine clearance ≤ 30 ml/min);
5) Patient unable to follow procedures, visits, examinations described in the study;
6) Any usual formal indication against imaging examinations (important claustrophobia, pacemaker);
7) History of another malignancy in the previous 2 years, with a disease-free interval <2 years. Patients with prior history of in situ cancer or basal or squamous cell skin cancer, any time prior to screening, are eligible.
8) OPTUNE device is not permitted in the study;
9) Patients cannot participate to any clinical trials utilizing a liquid biomarker or imaging studies that impact the overall survival.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

4.1 Treatment plan

Participants with recurrent GBM and recurrent WHO grade III glioma will be registered to the trial and have tumor biopsy samples undergo CSCs chemosensitivity testing with multiple FDA approved chemotherapeutic agents.

Participants will be ***randomized*** to a standard treatment arm (**Arm 1**) with chemotherapy chosen by the Physician from the provided list or to a study arm (**Arm 2**) of FDA-approved drugs selected by the ChemoID drug response assay.

Routine clinical assessments including history, physical exam, and lab assessments prior to treatment with chemotherapy should be performed based on standard of care (i.e. assessment prior to Day 1 of chemotherapy cycle) and as often as deemed necessary per treating physician discretion. Reporting of these routine clinical assessments is not necessary unless there are delays in treatment or dose modifications. These visits should be recorded as an Unscheduled Visit.

4.2 Duration of therapy

Participants enrolled to the standard of care chemotherapy or the ChemoID arms will continue treatment until unacceptable toxicity, hospice or death, or consent withdrawal.

In Arm 1 - the patient should continue therapy until unacceptable toxicity, hospice or death, or consent withdrawal. At every progression confirmed by RANO criteria, the treatment plan will change as per the physician choice.

In Arm 2 - the patient should continue therapy until unacceptable toxicity, hospice or death, or consent withdrawal. At every progression confirmed by RANO criteria, the treatment plan will change as per as per the ChemoID assay.

Alternatively: Arm 1 and 2 -: The number of cycles will be left up to the treating physician's discretion. However, patients should receive a minimum of 4 cycles of therapy and ideally treated until unacceptable toxicity, hospice or death, or consent withdrawal.

At the time of unacceptable toxicity or progression with the chemotherapy chosen from the ChemoID assay, treatment can be switched to ChemoID-based next chemotherapeutic agent or combination in Arm 2.

Bevacizumab is allowed in the clinical trial. If indicated it should be initiated at least 4 weeks post craniotomy or biopsy if the wound has healed well without any drainage or cellulitis. Bevacizumab is not expected to improve overall survival. On Bevacizumab the response to treatment and pseudo-response will be evaluated by each institution current radiographic assessments guidelines.

Re-radiation is allowed at any point at least 2 weeks postsurgical procedure, if the wound has healed well without any drainage or cellulitis

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Hospice or patients' death
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

CT scan or MRI will be performed as standard of care for the entire time patients are in the trial, and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments will be discontinued once patient is off of the clinical trial, hospice or death. Patient will be followed for the overall survival on or off the clinical trial.

4.3 Treatment window

A patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for *major life events* (e.g., serious illness in a family member, major holiday, vacation which is unable to be scheduled).

It will be acceptable for individual chemotherapy doses to be delivered within a "24 hour window before and after the protocol-defined date" for "Day 1" treatment of weekly treatment or 21- or 28- day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through Monday (day 3 past due).

4.4 ARM 1 - Physicians Choice of chemotherapy regimens

Patients randomized to the physician choice chemotherapy arm may be treated with one of the regimens specified in **section 8.1** per investigator discretion. Patients should receive treatment per standard practice and may continue on treatment until hospice or as per investigator discretion if having continued response (SD, PR or CR) and/or clinical benefit. The number of cycles of therapy should be administered as clinically appropriate, although it is suggested that patients should receive at least 4 cycles of therapy.

4.5 ARM 2 – ChemoID Drug Response Assay chemotherapy regimens

The physician will choose treatment regimen based on ChemoID drug response assay results on cancer stem cells (CSC) and bulk of tumor cells. Ideally, the regimen with the highest percentage cell kill for cancer stem cells and bulk of tumor combined should be used, however the physician has the flexibility to choose the best regimen according to anticipated patient tolerability. The regimens tested by the ChemoID drug response assay are the same as the one that can be chosen by the Physician for patients enrolled in Arm 1.

The dosing of the chemotherapy can be modified as per physician discretion. At the time of progression with the first agent from ChemoID assay, treatment can be switched to ChemoID based next chemotherapeutic agent or combination. Bevacizumab is allowed in the clinical trial. If indicated it should be initiated at least 4 weeks post craniotomy or biopsy if the wound has healed well without any drainage or cellulitis. Bevacizumab is not expected to improve overall survival (10, 11). On Bevacizumab the response to treatment and pseudo-response will be evaluated by each institution's current radiographic assessments guidelines.

Re-radiation is allowed at any point at least 2 weeks postsurgical procedure, if the wound has healed well without any drainage or cellulitis.

4.6 Duration of Study

Participants enrolled to the standard of care chemotherapy or the ChemoID arms will continue treatment until hospice or death, unacceptable toxicity, or consent withdrawal. Patients will receive chemotherapy as per standard of care regimens. The number of cycles will be per the investigator's discretion. After completion of chemotherapy, patients will

continue on active surveillance every month. The patient may voluntarily withdraw from the study at any time.

4.7 Follow-up after study treatment discontinuation

Participants enrolled to the standard of care chemotherapy or the ChemoID arms will continue follow up until death or consent withdrawal.

5 STUDY PROCEDURES

See Table 1 for the procedures and assessments to be performed during this phase of the study. All screening visit tests and procedures will occur within 14 days of the signed informed consent (IC). No screening exams will take place until the patient is fully informed of the research and signs the informed consent. This visit may take place over more than one day. Any MRI or CT scans done under standard of care are acceptable to screen patients.

5.1 Screening Visit

See Table 1 for the procedures and assessments to be performed during this phase of the study. The Screening Phase will take place over a two-week period, and it may be split into two visits. The Screening Visit will be performed by the study investigator to determine if the patient is eligible for the study.

Following are the steps involved with this phase of the study:

- Physical Exam and Clinical Assessment
- Vital Signs
- Height and Weight
- Pregnancy test
- Laboratory tests
- Brain Imaging by MRI or CT scan preferentially with contrast
- Medical Record Review
- Prior/Concomitant Medications
- Clinical Laboratory Evaluation
- Review Inclusion/Exclusion criteria
- Informed Consent

5.2 Enrollment Contingency Plans

In order to take into account certain unexpected events that can disrupt the planned study schedule, enrolled participants who unexpectedly expire prior to surgery or who are otherwise withdraw from the study after the screening period but before surgery, may be replaced without limit.

5.3 Study Treatment Phase

See Table 1 for the procedures and assessments to be performed during this phase of the study. Informed consent will be obtained prior to any study related procedures being performed, including discontinuation of current therapy.

Participants with recurrent GBM will be registered to the trial. An MRI (or CT if patient is unable to have an MRI performed) of the brain with and without contrast will have been performed within 14 days of the screening visit.

Blood samples will be drawn as per standard-of-care and will be used to confirm eligibility based on clinical laboratory parameters. Females will have a urine or serum pregnancy test.

Under standard of care, eligible participants with recurrent GBM or grade III glioma will undergo surgical resection and biopsy. Fresh tissue tumor biopsies will be sent to Pathology to confirm diagnosis of GBM, MGMT gene methylation status, IDH-1/2 status, and a portion of the fresh biopsy will be sent to the ChemoID lab at the Cabell Huntington Hospital, WV to perform the drug response assay.

Shipment of samples to the ChemoID lab will be performed using a secure shipping container for biological samples and the FEDEX carrier using standardized procedure under CLIA and CAP regulations.

All recurrent GBM participants registered to the trial will be ***randomized*** using a computer generated process and placed in the appropriate study arm.

Participants will be treated according to the randomly assigned study arm:

(**ARM 1**) standard of care chemotherapy chosen by the physician

or

(**ARM 2**) ChemoID-guided therapy.

Drugs will be dispensed according to study arm. Drug compliance and adverse event assessment will be performed.

Following are the steps involved with this phase of the study:

5.3.1 Visit 1 – pre-op visit

- Physical Exam (conducted under standard of care)
- Vital Signs (conducted under standard of care)
- Under standard of care, any brain imaging by MRI or CT scan with and without contrast performed prior to biopsy.
- Laboratory tests (conducted under standard of care)
- Scheduling for Surgical Removal of the Tumor and biopsy for Pathological Diagnosis or Tumor Biopsy for Pathological Diagnosis, MGMT gene methylation status, IDH-1 mutation status, and for ChemoID (at the same time).
- Medical Record Review

5.3.2 Visit 2 post-op visit

- Physical Exam (conducted under standard of care)
- Vital Signs (conducted under standard of care)
- Brain Imaging by MRI or CT scan preferentially with contrast
- Review of Pathology report
- Review of MGMT methylation gene promoter status
- Review of IDH-1 mutation status
- Registration to the trial of recurrent GBM patients
- Randomization of patients to receive either standard of care chemotherapy chosen by the physician (ARM 1) or ChemoID guided therapy (ARM 2).

5.3.3 Visit 3 post-radiation visit

- Physical Exam (conducted under standard of care)
- Vital Signs (conducted under standard of care)
- Under standard of care, Brain Imaging by MRI or CT scan preferentially with contrast

5.3.4 Visit 4 start of treatment visits

- Physical Exam (conducted under standard of care)
- Vital Signs (conducted under standard of care)
- Laboratory tests (conducted under standard of care)
- For participants randomly assigned to ChemoID guided therapy, review of ChemoID test results
- Start study intervention by dispensing study drug according to study arms' assignment and their cohorts
- Assess possible adverse events
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues to be completed before treatment start.

5.4 Follow-up Phase

See Table 1 for the procedures and assessments to be performed during this phase of the study. Participants will be followed for three years according to standard-of-care intervals by neurologic and neurosurgical clinical assessments as detailed in Table 1: schedule of study procedures.

Participant will be assessed at follow-up visits following standard-of-care radiation and surgery treatments and chemotherapy drugs will be dispensed according to groups and cohorts. Drug compliance and adverse event assessment will also be performed.

Outpatient visits will be completed as close to the scheduled visit dates as possible. The visit window is ± 7-14 days from the intended date of the visit. If needed, outpatient visit procedures may require more than one day to complete, if so, the date of the history and physical exam will be considered the visit date.

Follow-up visits consist of a clinical evaluation with particular attention to neurological function, seizures and corticosteroid use as per standard-of-care management of the disease. HRQoL. Laboratory tests of blood counts, glucose level, and blood count, liver function tests are indicated if the participant is receiving chemotherapy, corticosteroids and anti-epileptic drugs.

Labwork and brain imaging collected at visits as per standard-of-care.

At 6 and 12 months after Visit 24 there will be a phone call to assess survival status.

Following are the steps involved with this phase of the study:

5.4.1 Visit 1

- Physical Exam
- Vital Signs
- Laboratory tests if performed as per standard of care
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.2 Visit 2

- Physical Exam
- Vital Signs
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.3 Visit 3

- Physical Exam
- Vital Signs
- Laboratory tests if performed as per standard of care

- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.4 Visit 4

- Physical Exam
- Vital Signs
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.5 Visit 5

- Physical Exam
- Vital Signs
- Laboratory tests if performed as per standard of care
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.6 Visit 6

- Physical Exam
- Vital Signs
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.7 Visit 7

- Physical Exam
- Vital Signs
- Laboratory tests if performed as per standard of care
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.8 Visit 8

- Physical Exam
- Vital Signs
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts

- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.9 Visit 9

- Physical Exam
- Vital Signs
- Laboratory tests if performed as per standard of care
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.10 Visit 10

- Physical Exam
- Vital Signs
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.11 Visit 11

- Physical Exam
- Vital Signs

- Laboratory tests if performed as per standard of care
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.12 Visit 12:

- Physical Exam
- Vital Signs
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Continue study intervention according to study arms' assignment and their cohorts
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.13 Visits 13 to 23

Repeat as visits 1-11 schedules

5.4.14 Visit 24

- Physical Exam
- Vital Signs
- Laboratory tests if performed as per standard of care
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care if indicated
- Continue study intervention according to study arms' assignment and their cohorts

- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.4.15 Follow-up phone calls

- At 6 and 12 months following Visit 24 there will be a phone call to assess survival status.

5.5 Unscheduled Visits

Unscheduled visits will be handled as part of standard-of-care visits. Participant will be assessed by:

- Physical Exam
- Vital Signs
- Laboratory tests if performed as per standard of care
- Brain Imaging by MRI or CT scan preferentially with contrast if performed as per standard of care
- Medical Record Review
- Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

5.6 Concomitant Medication

Record all concomitant (OTC & prescription) taken 30 days prior to the screening visit through study termination.

5.7 Rescue Medication Administration

N/A

5.8 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, and AEs. The Investigator or the Sponsor

may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

5.8.1 Early Termination Study Visit

Subjects who withdraw from the study will be requested to have all procedures enumerated for Visit 24 as the early termination visit.

6 STUDY EVALUATIONS AND MEASUREMENTS

All laboratory exams and imaging monitoring procedure, measurements and therapeutic interventions listed in Section 4 will be done following standard-of-care procedure.

Better Health-Related Quality of Life (HRQOL) will be assessed using standardized self-reported, and validated questionnaires, addressing physical, psychological, emotional, and social issues.

6.1 Screening and Monitoring Evaluations and Measurements

6.1.1 Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).

- Age
- Gender
- Weight
- Pathology report
- Steroid and other medication doses over the course of treatment
- ChemoID test results
- MGMT gene methylation status
- IDH-1 mutation status
- Chemotherapy regimens including doses
- Radiation therapy schedule and doses

- All brain imaging including but not limited to DICOM images of MRI and or CT scans as well as reports
- Clinical assessment of disease at baseline and during the course of therapy from neuro-oncologic progress notes
- Health-Related Quality of Life (HRQOL) questionnaires addressing physical, psychological, emotional, and social issues.

6.1.2 Physical Examination

Medical history, height and weight, physical examination by neurological exam, demographic characteristics (age, gender, race) will be performed and collected.

6.1.3 Vital Signs

Blood pressure will be measured with an automated device or with an aneroid sphygmomanometer on the right arm with patient sitting.

6.1.4 Laboratory Evaluations

Blood sampling will be performed for the following laboratory evaluations:

6.1.4.1 Hematology

*Hematology testing will be performed at the laboratory at the investigators institution (*Blood *c*ollection of both CMP and CBC with Differential within 7-days prior to starting Temodar. Blood collection weekly during treatment, and then weekly for 3 more weeks after chemotherapy stops. Then SOC is every 2 weeks for labs).

Table: Clinical Laboratory Tests

Category	Tests
Hematology	RBC, hemoglobin, hematocrit, platelet count, WBC with differential
	blood glucose levels
Liver function tests	Complete metabolic panel
Renal function tests	Complete metabolic panel

6.1.4.2 Pregnancy Testing

A urine or a serum pregnancy test will be performed for female subjects ≥ 18 years of age who are physically capable of becoming pregnant.

6.1.5 Other Evaluations, Measures

Other evaluations will concern review of brain Imaging by MRI or CT scan preferentially with contrast, pathology report, MGMT methylation gene promoter status, IDH-1 mutation

status, ChemoID assay test results, Better Health-Related Quality of Life (HRQOL) assessment based on questionnaires, addressing physical, psychological, emotional, and social issues.

6.2 Efficacy Evaluations

Under standard-of-care, clinical response to therapy will be evaluated according to the 2D Response Assessment in Neuro-Oncology (RANO) criteria, in which in addition to contrast enhancement, tumor extension on T2- and fluid-attenuated inversion recovery (FLAIR)-weighted MRI are evaluated (8). Furthermore, an assessment of neurological function and corticosteroid use will be included.

6.3 Safety Evaluation

Subject safety will be monitored by adverse events, vital signs, physical examinations, and clinical laboratory data.

However, the ChemoID assay is considered a non-significant risk (NSR) assay for the patients because the drugs prescribed to the participants are part of the standard-of-care practice for the treated disease. Any side effects from administering chemotherapies are not associated with the assay per se. Any morbidity associated with tissue sampling is also part of standard-of-care and its expected risks are not associated with the assay.

7 STATISTICAL CONSIDERATIONS

7.1 Primary Endpoint

The primary endpoint of this study is:

- Median Overall Survival (OS)

7.2 Secondary Endpoints

Secondary endpoints will include the following:

- Overall Survival at 6, 9, and 12 months (OS_{6mo}, OS_{9mo}, OS_{12mo})
- Median Progression Free Survival (PFS)
- Progression Free Survival at 4, 6, 9, and 12 months (PFS_{4mo}, PFS_{6mo}, PFS_{9mo}, PFS_{12mo})
- Objective tumor response measured by RANO (Response Assessment in Neuro-Oncology Criteria)
- Time to recurrence
- Health-Related Quality of Life (HRQOL)

7.3 Statistical Methods

7.3.1 Baseline Data

Initial analyses will involve data cleaning, variable development, and exploratory data analyses. We will use standard summaries to describe baseline characteristic distributions in terms of centrality, spread, shape, and possible outliers by arm, cohort and treatment group. Graphical explorations will emphasize examination of the nature and extent of potential nonlinear relationships on the appropriate modeling scale (e.g. natural, log, logit, etc.)

7.3.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects randomized at baseline. The primary efficacy outcome is overall survival (OS) in months. This outcome will be compared between patients randomized to ChemoID guided chemotherapy (ChemoID) versus standard of care (SOC). OS comparisons will be examined using Cox Proportional Hazard Models for Overall Survival with baseline hazards stratified by site and medians will be compared between treatment arms. Models examining adjustments for sex, race, age, and tumor stage will be constructed, as well as for moderating effects of these variables (subpopulation investigations).

Secondary analyses will include logistic regression models for Overall and Progression Free Survival at 4, 6, 9, and 12 months, Cox Proportional Hazard Models for Progression Free Survival in months, Generalized Linear Models (GLMs) for analyses on objective tumor response (RANO), and Health-Related Quality of Life (HRQOL). Generalized Linear Mixed Models (GLMMs) will be used for analyses of changes in any additional repeated outcome measures to incorporate within-person associations and examine distributions of participant-specific declines. Huber-White robust standard errors will be used, and multiple variance structures will be investigated to examine sensitivity of primary analyses to the choice of association model. Shared Parameter Models (SPM) will be used to examine any potential informative missing data effects.

7.3.3 Safety Analysis

All evaluable subjects entered into the study at Baseline will be included in the safety analysis. AE/SAE frequencies and probabilities and confidence intervals will be compared between the treatment groups.

7.4 Sample Size and Power

For our primary analyses comparing median Overall Survival (OS), with N=150, a 1:1 ratio between treatment groups, an overall alpha rate of 5% and interim analysis described below, we will have over 80% power to detect a relative decrease in in the hazard of mortality of HR $\leq$ 0.55 or more at the final analysis.

7.5 Interim Analysis

Interim analyses are based upon the alpha spending approach of Lan and DeMets. According to the established final sample size and assumed 105 primary events needed for the final analysis. We will conduct two planned interim analyses. One will be triggered when 35 patients have died. The trial may be stopped for efficacy at this point if both the observed HR is less than or equal to 0.55 and its associated p-value $\leq$ 0.0167. Assuming the trial moves forward, the second interim analysis will occur once 70 participants have died. The trial may be stopped for efficacy at this point if both the observed HR is less than or equal to 0.55 and its associated p-value $\leq$ 0.0218. The final analysis will occur at 105 deaths, and the nominal p-value to declare efficacy will be 0.0278.

8 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

8.1 Description

This clinical study utilizes FDA approved chemotherapies that are currently used for the treatment of recurrent Glioblastoma and recurrent WHO III Glioma. Following is a table illustrating the list of chemotherapy agents used in this study.

List of Current Chemotherapeutic Agents and suggested Combinations on the ChemoID® GBM Drug Panel

	Single Drug	**Dose**
1	Carboplatin	350 mg/m2 or 4 AUC
2	Irinotecan	125 mg/m2
3	Etoposide	50 mg/m2
4	BCNU	100 mg/m2
5	CCNU	100 mg/m2
6	Temozolomide	150-200 mg/m2
7	Procarbazine	60 mg/m2
8	Vincristine	1.4 mg/m2
9	Imatinib	400 mg
	Drug Combination	**Dose**
1	Procarbazine CCNU Vincristine	60 mg/m2 100 mg/m2 1.4 mg/m2
2	Carboplatin Irinotecan	350 mg/m2 or 4 AUC 125 mg/m2
3	Carboplatin Etoposide	350 mg/m2 or 4 AUC 50 mg/m2
4	Temozolomide Etoposide	50 mg/m2 50 mg/m2
5	Temozolomide Imatinib	50 mg/m2 200 mg

9 SAFETY MANAGEMENT

The ChemoID assay is a low risk assay for the patients. Any side effects from administering chemotherapies are not associated with the assay per se. Any morbidity associated with the sampling is part of standard-of-care and its expected risks are not associated with the assay. We will record and report only adverse events of grade 3 and 4.

9.1 Clinical Adverse Events

Clinical adverse events due to standard-of-care drugs (AEs) will be monitored throughout the study. This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

9.1.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (attribution of unrelated, unlikely, possible, probable, or definite (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

Following is a definition of the meaning of each Adverse Events term.

Grades: Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3 Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

9.1.1.1 Percentage of frequency of potential adverse events and serious events related to chemotherapy drugs used in this study

Carboplatin	Irinotecan	Etoposide	BCNU	CCNU
Leukopenia (26-97%)	Anemia (>90%)	Leukopenia (60-91%)	Convulsions (19%)	Nausea (54%)
Neutropenia (21-96%)	Leukopenia (>90%)	Nausea and Vomiting (30-40%)	Hemiplegia (19%)	Vomiting (54%)
Nausea (81-93%)	Neutropenia (>90%)	Thrombocytopenia (28-41%)	Headache (15%)	Neurotoxicity
Vomiting (81-93%)	Thrombocytopenia (>90%)	Alopecia (20-90%)	Metabolic disorder (14%)	Myelosuppression (delayed 4-5 weeks)
Anemia (14-90%)	Elevated bilirubin (88%)	Anorexia (13%)	Somnolence (14%)	Ataxia
Magnesium loss (43-61%)	Diarrhea (85%)	Diarrhea (13%)	Fever (12%)	Lethargy
Thrombocytopenia (33-66%)	Nausea (79%)	Leukopenia (60-91%)	Confusion (10%)	Disorientation
Alopecia (2-49%)	Asthenia (70%)	Anemia (≤33%)	Aphasia (9%)	Stomatitis
Asthenia (11-41%)	Abdominal pain (63%)	Pancytopenia (7%)	Nausea (8%)	Mucositis
Elevated alkaline phosphatase (29-37%)	Vomiting (60%)	Stomatitis (6%)	Vomiting (8%)	Pulmonary fibrosis (rare)
Central neurotoxicity (5-26%)	Alopecia (43%)	Hepatic toxicity (3%)	Pain (7%)	Pulmonary toxicity
Elevated AST (19-20%)	Fever (42%)	Type 1 hypersensitivity (2%)	Rash (5%)	Elevated LFTs
Peripheral neuropathy (6-15%)	Constipation (41%)	Orthostatic hypotension (1-2%)	Abscess (4%)	Leukemia
Immune hypersensitivity reaction (2-9.2%)	Anorexia (34%)	Peripheral neuropathy (1-2%)	Cranial edema (4%)	Renal toxicity
Elevated bilirubin (5%)	Mucositis (32%)		ICP elevation (4%)	Hepatic toxicity
	Pain (31%)		Meningitis (4%)	Infertility
	Dyspnea (28%)		Hyperglycemia (3%)	Alopecia
	Cough (27%)		HTN (3%)	Optic atrophy (rare)
	Dizziness (23%)		Constipation (2%)	
	Infection (22%)		Diarrhea (2%)	
	Rash (19%)		Dizziness (2%)	
	Abdominal fullness (10%)		Depression (2%)	
	AST increased (10%)		Greater myelotoxicity reported when co-administered with cimetidine	

	Dyspepsia (10%),		Cardiac disorders: Tachycardia and chest pain	
	Edema (10%)		Eye disorders: conjunctival edema, conjunctival hemorrhage, blurred vision and loss of depth perception	
	Ascites/jaundice (9%)		Gastrointestinal toxicity: Nausea, vomiting, anorexia, and diarrhea	
	Vasodilation (9%)		Hepatotoxicity: Increased transaminase, increased alkaline phosphatase, increased bilirubin levels Infections and Infestations:	
	Thromboembolism (9%)		Infections: Opportunistic infections (including with fatal outcome)	
	Hypotension (6%)		Neoplasms benign, malignant and unspecified (including cysts and polyps): Acute leukemia, bone marrow dysplasia	
	Neutropenic fever (2-6%)		Nephrotoxicity: Progressive azotemia, decrease in kidney size, renal failure	
			Nervous system disorders: Headaches, encephalopathy, and seizures	
			Pulmonary toxicity: Pneumonitis, interstitial lung disease	
			Reproductive system and breast disorders: gynecomastia	
			Skin and subcutaneous tissue disorders: Burning sensation, hyperpigmentation, swelling, pain, erythema, skin necrosis, alopecia, allergic reaction	
			Vascular Disorders: Veno-occlusive disease	

Temozolomide	**Procarbazine**	**Vincristine**	**Imatinib**
Alopecia (55-69%)	Neuropathy	Alopecia (20-70%)	Edema (53%)
Lymphopenia (55%)	Neurotoxicity	Peripheral neuropathy	Neutropenia (Grade 3: 7-27%; Grade 4: 3-48%)
Nausea (53%)	Nausea	Paresthesia	Nausea (43%)
Vomiting (42%)	Vomiting	Sensory loss	Muscle cramps (35%)
Headache (41%)	Pleural effusion	Acute uric acid nephropathy	Musculoskeletal pain (34%)
Fatigue (34%)	Myelosuppression	Loss of deep-tendon reflexes	Thrombocytopenia (Grade 3: 1-31%; Grade 4: 1-34%)
Constipation (33%)	Heinz bodies	Hypertension	Rash (32%)
Anorexia (9-27%)	Hepatic dysfunction	Hypotension	Fatigue (31%)
Convulsions (23%)	Impairment of fertility	Nausea	Diarrhea (30%)
Thrombocytopenia (19%)		Vomiting	Headache (29%)
Rash (8-19%)		Constipation	Arthralgia (27%)
Hemiparesis (18%)		Paralytic ileus	Abd pain (23%)
Diarrhea (16%)		Myelosuppression	Myalgia (21%)
Neutropenia (14%)		Leukopenia	Nasopharyngitis (19%)
Fever (13%)		Gait changes	Hemorrhage (19%)
Asthenia (13%)		Jaw pain	Vomiting (15%)
Dizziness (12%)		Aspermia	Dyspepsia (15%)
Peripheral edema (11%)		Amenorrhea	Cough (13%)
Viral infections (11%)			Dizziness (13%)
Amnesia (10%)			URT infection (13%)
Insomnia (10%)			Fever (12%)
Abdominal pain (5-9%)			Weight gain (12%)
Ataxia (8%)			Hepatotoxicity (6-12%)
Back pain (8%)			Insomnia (11%)
Paresis (8%)			Hematologic toxicity (1-64%)
URI (8%)			Flushing
Urinary incontinence (8%)			Palpitation
UTI (8%)			Dry skin
Abnormal vision (5-8%)			Erythema
Pruritus (5-8%)			Metabolic hyperglycemia
Breast pain (6%)			Stomatitis/mucositis
Depression (6%)			Lymphopenia
Confusion (5%)			Congestive heart failure and left ventricular dysfunction
Myalgia (5%)			Hypereosinophilic cardiac toxicity
Weight gain (5%)			Aplastic anemia
Anemia (4%)			Atrial fibrillation
Erythema (1%)			Avascular necrosis

			Cardiac failure
			Cardiogenic shock
			Embolism
			Eosinophilia
			Hypothyroidism
			Growth retardation in children and adolescents
			Tumor lysis syndrome
			Impairments related to driving and using machinery

9.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with ASRI-WPAHS IRB SOP 011: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

10 STUDY ADMINISTRATION

10.1 Treatment Assignment Methods

Participants will be randomly assigned to the study arms according to their main characteristics:

Consented participants affected by resectable recurrent GBM or grade III glioma able to provide a fresh tumor biopsy.

10.1.1 Randomization

Participants will be randomized using a statistical random number generator using REDCap. Study investigators will be kept blind to the schedule. A password-protected web-portal (REDCap) will be available for study-personnel to access patient randomization assignments

10.1.2 Blinding

Investigators and trial personnel will not be aware of ChemoID test results for patients in ARM 1 (standard of care chosen by physician) until the end of the study. The ChemoID lab will not release test results for these subjects.

Investigators and trial personnel will request to the ChemoID lab the test results **only** for subject assigned to the ChemoID-guided therapy (ARM 2).

Subjects will be blinded to the arm they have been randomized to.

10.1.3 Unblinding

Not allowed

10.2 Data Collection and Management

Primary records (source documents) and case report forms (CRF) will be collected in paper format and subsequently entered to either Medidata Rave or REDCap, two secure cloud–based clinical data management systems used to electronically capture, manage, and report clinical research data. Both systems provide web-based case report forms, real-time data entry validation, audit trails, and the ability to set up a calendar to schedule and track critical clinical study events such as radiological imaging, participant visits, etc. In addition, the software allows identifying and protecting fields that contain Protected Health Information (PHI) data by employing user rights that are set by the study administrator to control who can view, modify, or add data and/or forms. All activities are system logged, and are available in a full audit trail. Confidentiality will be maintained by keeping a master list containing patient health information (PHI) by using a subject identification (ID) number that have only a study ID number. Both systems also offer a data export utility, which enables to export data in an automated manner into formats that are compatible with commonly used statistical analysis packages such as SAS, SPSS, Stata, and R.

10.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. ChemoID personnel are HIPAA trained and certified. No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers before sharing a limited dataset (PHI limited to dates and zip codes).

10.4 Regulatory and Ethical Considerations

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

Prior to initiating this study, this protocol will be reviewed and approved by the appropriate local IRB. The composition and conduct of this committee will conform to the United States CFR.

The IRB will also review and approve the site's informed consent form (ICF), other written information provided to the patient that may be used for patient recruitment.

If it is necessary to amend the protocol or the ICF during the study, the Investigator will be responsible for ensuring that the IRB reviews and approves these amended documents. An IRB approval of the amended protocol and/or ICF must be obtained in writing before implementation of the amended procedures and before new patients are consented to participate in the study using the amended version of the ICF.

10.4.1 Data and Safety Monitoring Plan

The ChemoID assay is a non-significant risk assay for the patients. Any side effects from administering chemotherapies are not associated with the assay per se. Any morbidity associated with the sampling is part of standard-of-care and its expected risks are not associated with the assay. This is a prospective randomized clinical study in which the risk of the participants is low
also because all the drugs used are already FDA approved to treat the specific disease. This clinical study is not evaluating the efficacy of the drugs, but the ability of the ChemoID test to predict drugs that will provide better outcomes to the patients who are treated with ChemoID guided therapy vs. subjects treated with empirically chose drugs.
Interim analyses will be conducted at times coincident with regularly scheduled meetings of the appointed Data and Safety Monitoring Board (DSMB) at approximately six-month intervals.

Only grades 3 or 4 SAE are reportable to the Sponsor. The Sponsor will notify the DSMB Chair each time a grade 3 or 4 SAE occurs. The DSMB will evaluate unblinded SAE data when 25 GBM patients have completed 1 month of follow-up (Visit 1). Other safety data, such as laboratory data will also be evaluated by the DSMB as appropriate. Monitoring of key safety endpoints will be conducted as described above, and if rates significantly exceed pre-set thresholds, ChemoID sponsor will be notified and information will be supplied to the DSMB. All SAEs, at least possibly related, will also be sent to the DSMB chair. The Project Officer (or designee) will be responsible for reviewing the SAE materials to determine if the documents are complete. If there are any concerns regarding the type or frequency of the event, the Project Officer will request that the DSMB Executive Secretary notify the DSMB Chair. The DSMB Chair will review the SAE materials, determine if the information is complete, determine if additional DSMB review is required and make recommendations to sponsor concerning continuation of the study. The data-coordinating center (DCC) will prepare semi-annual summary reports of all AEs/SAEs for the Project Officer and Chair. Semi-annual reports will be made available on a secure website and the Project Officer and DSMB Chair will be notified by e-mail when the materials are posted.

10.4.2 Risk Assessment

Risks for this study are not greater than minimal because the chemotherapy drugs used for treatments of participants in all the study arms are all FDA approved agents to treat recurrent glioblastoma and recurrent WHO III Glioma. Physicians treating participants enrolled in study arms and/or cohorts in which the treatment is guided by the ChemoID assay will

choose treatments from those indicated as high-cell kill from the test, but always taking into consideration the performance status and general clinical condition of the patients.

The adaptive design of the study will minimize the risks of harm to participants by providing the principal investigator the ability to suspend the study after 18 months, if higher than standard-of-care risk to therapeutic intervention will be identified.

10.4.3 Potential Benefits of Trial Participation

The information obtained from the test will be used to understand if the chemo sensitivity assay using CSCs in conjunction with the bulk tumor cells can help to achieve better outcomes in cancer patients.

Collectively, results of clinical response to empirical therapy or to chemotherapy agents suggested by chemosensitivity testing will be used to determine the predictive value of chemosensitivity testing to clinical response.

The potential direct benefits include better response to chemotherapy and clinical outcome as well as the possible avoidance of potentially ineffective, costly and morbidity producing chemotherapies. Indirect benefits include reducing the chance of ineffective chemotherapy, unnecessary hospitalizations, and lowering the health-care cost.

10.4.4 Risk-Benefit Assessment

Although there are several chemotherapy agents used to treat recurring GBMs and WHO III Gliomas, there is no standard of care treatment approved for these patients. Selection of effective chemotherapy is extremely important when therapy is first initiated. In fact, administration of ineffective anticancer therapy is associated with unnecessary toxicity and the development of more aggressive cancer cell clones that are resistant to subsequent therapies. The ability to initially choose the most effective chemotherapy may help to avoid the physical, emotional, and financial burden to patients of ineffective therapy, thereby improving their quality of life. Each time patients are treated, they have a chance of relapse, and their cancer will likely become more resistant to therapy. Presently used anticancer drugs have a high rate of failure, and cell culture chemotherapy testing has been used to identify which drugs are more likely to be effective against a particular tumor type. Measuring the response of the tumor cells to drug exposure is valuable in any situation in which there is a choice between two or more treatments ChemoID is the first and only drug response assay available in the clinics that examine CSCs that contribute to treatment resistance, and tumor recurrence from solid tumors.

Results from previous ChemoID clinical studies indicate that a drug response assay that targets specifically targets CSCs along with bulk tumor cells may be a very useful tool for optimizing treatment selection when first-line therapy fails and when there are multiple clinically acceptable and equivalent treatments available. Furthermore, the ChemoID study results indicate that individualized functional drug response assays provide more treatment options with improved outcomes for many recurrent patients than are currently achieved by

empiric population-based treatment. This data suggests that it is reasonable to prospectively utilize a functional test like ChemoID drug response assay to assist clinicians in the optimal prioritization of therapy for recurring GBM and WHO III Glioma patients.

10.5 Recruitment Strategy

Patients coming to clinical visit and/or neuro-oncologic consult for symptoms and/or imaging findings related to the presence of a recurring glioblastoma will be approached as eligible subjects for the study. Following a discussion on their medical treatment options, candidates will sign an informed consent to be enrolled in the study. Subjects will be included in the study if the pathology report of their tumor biopsy will confirm the presence of recurrent glioblastoma multiforme.

10.6 Informed Consent/Assent and HIPAA Authorization

Before being admitted to the clinical study, all patients will consent in writing to participate. Informed consent may be obtained from a legal authorized representative when the person is not competent, incapacitated, or otherwise unable to make an informed judgment. An informed consent form (ICF) will be given to each patient, which will contain all United States federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act (HIPAA) authorization information in language that is understandable to the patient.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

The Investigator will review the study with each patient. The review will include the nature, scope, procedures, and possible consequences of the patient's participation in the study. The ICF and review will be in a form understandable to the patient. The Investigator or designee and the patient must both sign and date the ICF after review and before the patient can participate in the study. The patient will receive a copy of the signed and dated form, and the original will be retained in the site study files. The Investigator or his/her designee will emphasize to the patient that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The site must use the amended consent form for all new patients and repeat the consent process with the amended ICF for any ongoing patients.

Patients' names will remain confidential and will not be included in the database. Only patient number, patient initials, and birth date will be recorded in the data system. If the patient name appears on any other document collected (e.g., hospital discharge summary), the name will be obliterated before the document is transmitted. All study findings will be

stored in paper format databases. The patients will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB to inspect their medical records to verify the information collected.

Patients will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws, including, without limitation, the HIPAA.

All participants in the will provide written authorization to disclose private health information either as a part of the written ICF or as a separate authorization form. The authorization will contain all required elements specified by 45 CFR 164, and will contain a waiver of patient access to study-related private health information until the conclusion of the clinical study. The authorization will remain valid and in full force and effect until the first to occur of (1) the expiration of 2 years after the study therapy is approved for the indication being studied, or (2) the expiration of 2 years after the research program is discontinued. Individual patient medical information obtained during this study is confidential and its disclosure to third parties (other than those mentioned in this Section 9.7) is strictly prohibited. In addition, medical information obtained during this study may be provided to the patient's personal physician or to other appropriate medical personnel when required in connection with the patient's continued health and welfare.

The Investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified. Confidentiality will be maintained by keeping a master list containing patient health information (PHI) and subject identification (ID) number separate from paper data forms that have only a study ID number. The master list will be on a separate computer, removable disk drive or in a locked file cabinet and therefore, this form of data is considered “coded”.

11 PUBLICATION OF CLINICAL DATA

Patient data collected will be examined and analyzed independently by a group of radiologists and biostatisticians.

Complete trial data and end of study statistics will be provided to the principal investigators of the multicenter clinical study and the publication write up will be done in collaboration between the investigators.

12 REFERENCES

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APPENDIX

1. Informed Consent (IC)

INFORMED CONSENT FORM AND AUTHORIZATION TO DISCLOSE PROTECTED HEALTH INFORMATION FOR A RESEARCH STUDY

TITLE:	Standard Chemotherapy versus Chemotherapy Chosen by Cancer Stem Cell Chemosensitivity Testing in the Management of Patients with Recurrent Glioblastoma Multiforme (GBM).
PROTOCOL NO.:	CG01-GBM WIRB® Protocol #20172720
SPONSOR:	ChemoID
INVESTIGATOR:	Tulika Ranjan, MD Allegheny Cancer Center 5th Floor Allegheny General Hospital 320 E. North Avenue Pittsburgh, PA 15212 United States
STUDY-RELATED PHONE NUMBER(S):	Tulika Ranjan, MD 412-770-3039 (24 Hours)

1 - ***Introduction*:** You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. There may be risks associated with being part of research studies. If there are any risks involved in this study then they will be described in this consent. Your participation is voluntary. Please take your time to make your decision, and ask your research doctor or research staff to explain any words or information that you do not understand.

2 - What you should know about a research study:

- Someone will explain this research study to you.
- You volunteer to be in a research study.
- Whether or not you take part is up to you.
- You can choose not to take part in the research study.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- Feel free to ask all the questions you want before you decide.

3 - Who can I talk to if I have questions?

If you have questions, concerns, or complaints, or think the research has hurt you, you should contact the principal investigator – Tulika Ranjan, MD, 412-770-3039, she can be reached 24 hours/day.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research or for any of the reasons listed below:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research

You may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

If you have any questions regarding Allegheny Health Network Research, please contact 1-844-577-4621.

4 - Why is this study being done?

The investigational purpose of this study is to screen chemotherapy drugs currently used for the care of recurrent glioblastoma (a form of brain cancer) and to determine the most effective treatment based on results from a chemosensitivity assay.

Chemosensitivity drug assay refers to testing a patient's own cancer cells in the laboratory to drugs that are to be used to treat the patient's cancer.

Following surgery, you will be treated either as per chemotherapy agents chosen by the physician or with chemotherapies as suggested by the results of the chemosensitivity testing.

We would like to determine if patients treated with drugs predicted by the chemosensitivity test have better outcomes than patients treated with drugs chosen by the treating physician.

5 - How long will the research last?

We expect that you will be in this research study for 3 years. This study is designed to follow you for long-term survival as such – your doctor and his/her staff would like to follow your long-term health status for a period of not more than 36 months, by accessing your hospital records.

You can decide to stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff to discuss what follow up care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped. If you decide to withdraw or if you are removed from the study, all data generated up to the date of withdrawal from the study will be collected.

6 - How many people will be studied?

About three hundred (300) people will take part in this study over a three year period. Allegheny Health Network is projected to enroll 60 participants per year in the trial; two additional sites are projected to enroll 40 participants per year.

7 - What happens if I say yes, I want to be in this research?

This study uses sample specimens obtained by the same surgical procedures that patients have to routinely undergo for the treatment of recurrent brain cancer.

Surgical resections are part of the established standard-of-care procedures to treat recurrent brain cancer. You will be asked to sign a separate consent form for this procedure as per standard of care.

As per standard-of-care, tumor biopsies from the surgical resections will be sent to the pathology laboratory for pathological confirmation of recurrent GBM and for MGMT methylation status assessment.

Biopsies will be also sent to the ChemoID laboratory for drug response assay assessment, which is a laboratory-developed test (LDT).

Participants will be randomized to receive either ChemoID guided chemotherapy with standard-of-care drugs, or standard-of-care drugs chosen by the Physician.

A computer will choose the treatment-group that you are assigned. Neither you nor the study doctor will choose what treatment-group you will be assigned. You will have one in two chance of being assigned to each treatment-group. You will not be told in which treatment-group you are, however your study doctor will know.

All diagnostic procedures (except for ChemoID test), therapeutic management and follow-up procedures will be conducted under standard-of-care for the disease.

- Administration of chemotherapy drugs will be under standard-of-care management of the disease.
- Follow-up visits will consist of a clinical evaluation with particular attention to neurological function, seizures and corticosteroid use, as per standard-of-care management of the disease.
- Indicated laboratory tests of blood counts, glucose level, and blood count, liver function tests, and the administration of corticosteroids and anti-epileptic drugs will be as per standard-of-care management of the disease.
- Radiological imaging with CT and/or MRI preferentially with contrast will be performed every 2 months as per standard-of-care management and follow-up of the disease.

8 - What happens if I say no, I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

9 - What happens if I say yes, but I change my mind later?

If you agree to take part in the research now and stop at any time it will not be held against you. You may discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled.

10 - What are the risks of the study?

Being in this study involves some risk to you, which are the same as the risks listed on your surgical consent. You should discuss with the study staff the risks of being in this study, which are the same as the risks of being treated with standard-of-care chemotherapy and radiation.

You should talk to your study doctor about any side effects that you have while taking part in the study. You will be provided with a US Package insert listing the risks and side effects for each drug that you will receive. Again, feel free to discuss with the study doctor this information and ask any questions about anything you feel needs to be explained to you.

There may be side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

PREGNANCY
Pregnant women or nursing mothers cannot participate in the study. Women of childbearing age must have a negative pregnancy test within 72 hours prior to study entry. Women of childbearing potential must practice medically approved contraceptive precautions. The study doctor will explain the pregnancy risks and the length and precautions you will need to take (depending of the treatment drugs you will be assigned to) not to become pregnant.

11 - Will being in this study help me anyway?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include prolonged response to treatment. Also, we hope the information learned from this study will benefit other people in the future.

12 - What other choices are there?

You do not have to be in this study to receive treatment. You may still receive the same chemotherapy treatments without being in the study.

The study doctor will discuss your alternative treatments option with you including comfort care.

If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

13 - Will my information be kept confidential?

Your identity and medical records and data related to this study will be kept confidential, except as required by law and except for inspections by the Department of Health and Human Services, the Food and Drug Administration the sponsor (ChemoID), Allegheny Health Network, the Allegheny Health Network Research Institute, the Institutional Review Board (the committee that reviews, approves and oversees research) and the AHN Compliance Office. By law, anyone who looks at your records must keep them completely confidential. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.

Results of the research may be published for scientific purposes or presented to scientific groups; however, your identity will not be revealed.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Federal law provides additional protections of your personal health information. These are described below in the **HIPAA Authorization Section below.**

14 - Can I be removed from the research without my OK?

The investigator in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include failure to follow instructions of the research staff or if the investigator in charge decides that the research study is no longer in your best interest. The sponsor can also end the research study early.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

15 - Are there costs of taking part in this study?

There are no costs to you for taking part in this study. The chemosensitivity assay that is required for this study will be provided to you at no cost and will be paid for by the study sponsor, ChemoID.

Costs for your regular medical care, which is not related to this study, will be your own responsibility. This kind of research study is not expected to result in any additional costs to you or your insurance company. If you require medical care for your glioblastoma or other health problems, as part of your routine care (care you receive even if you do not participate in this research study), either you or your insurance carrier will be billed for these charges. The cost for the standard-of-care items will be billed to you or your insurance company as usual. If you require additional medical care for your glioblastoma or other health problems, as part of your standard medical care, either you or your insurance carrier will be billed for these additional charges. Please talk with the study doctor about any expected costs or health insurance problems.

16 - Will I be paid to participate in this study?

You will not be paid for your participation in this research study.

17 - What if I am injured while taking part in this study?

If you are injured or made sick while taking part in this research study, emergency medical treatment will be provided at the usual charge. No funds have been set aside by Allegheny Health Network or Allegheny Health Network Research Institute to pay you in case you are injured. You do not waive any of your legal rights to compensation, if any, by signing this form.

18 - What are my rights as a research study participant?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

19 - Authorization to Use and Disclose Individually Identifiable Health Information for a Research Study

Before you can take part in this research study, the Allegheny Health Network is required to obtain your authorization to use and/or disclose (release) your health information. This section describes to you how, and to whom, your health information will be used and/or disclosed (shared) while you are participating in this research study. It is important that you read this carefully. Allegheny Health Network and its' researchers are required by law to protect your health information.

The following is a list of health information that will be used and/or disclosed:

- Age
- Gender
- Weight
- Pathology report
- Record of steroid and other medication doses over the course of treatment
- ChemoID test results
- MGMT gene methylation status
- IDH-1 mutation status
- Chemotherapy regimens including doses
- Radiation therapy schedule and doses (if part of therapy regimen)
- All brain imaging including but not limited to DICOM images of MRI and or CT scans as well as reports
- Clinical assessment of disease at baseline and during the course of therapy from neuro-oncologic progress notes
- Health-Related Quality of Life (HRQOL) questionnaires addressing physical, psychological, emotional, and social issues.

The following is a list of entities that may use and/or disclose your health information as part of this study:

<u>Internal Oversight</u>
Those who oversee the study will have access to your health information, including the following:

- Allegheny Health Network (AHN)
- Allegheny Health Network Research Institute
- AHN Compliance Office
- Study Doctor and Study Staff

<u>Governmental Oversight</u>
Your health information may also be shared with government agencies that have oversight of the study or to whom access is required under the law:

- Department of Health and Human Services (DHHS)
- Food and Drug Administration (FDA)

Others Outside Allegheny Health Network

The following persons and/or organizations outside of Allegheny Health Network may also use, disclose and receive your health information in connection with this study:

- Sponsor (and companies owned/affiliated with sponsor): ChemoID may need to view your medical records to make sure the study is being completed correctly.
- Western Institutional Review Board® (WIRB®) is a group of people who review the ethics of human research.
- A Data Safety Monitoring Board (DSMB) will be responsible to monitor data quality management and ongoing assessment of safety.
- ChemoID laboratory at the Translational Genomics Research Institute (TGRI) in Cabell Huntington Hospital will test patient's own cancer cells to drugs that are to be used to treat the patient's cancer.

In order to participate in this study, you must agree to share your health information with the persons and organizations listed above. If these persons or organizations that you authorize to receive and/or use protected health information, are not health plans, covered health care providers or health care clearinghouses subject to federal health information privacy laws, they may further disclose the protected health information and it may no longer be protected by the federal health information privacy laws.

Expiration of Authorization

This authorization will not expire unless you revoke it in writing. You may revoke or end this authorization by writing to the Principal Investigator:

Tulika Ranjan, MD
Allegheny Health Network
320 East North Avenue
Pittsburgh, PA 15212

If you revoke your authorization, you will also be removed from the study. Revoking your authorization only affects the use and sharing of your health information after the written request is received. Any health information obtained prior to receiving the written request may be used to maintain the integrity of the study.

Authorization
By signing this document (authorization), you authorize that your health information can be used and/or disclosed as described.

Your access to your protected health information created or obtained by Allegheny Health Network in the course of the research (that includes treatment) may be temporarily suspended for as long as the research is in progress. By signing this document, you are agreeing to the denial of access to your protected health information, created for the research, while you are participating in this research study. Your access to your protected health information will be reinstated upon completion of the research.

If you choose to not sign this document, you will not be permitted to participate in this research study.

20 - Consent for Future Use of Specimens

We would like to keep your specimens that are left over from the study for future research. Reports about future research will not be given to you or your regular doctor. These reports will **not** be put in your health record.

The specimens will be coded in such a manner that it should not be possible for others to find out that they came from you.

Even if you decide now that your specimens can be used for future research, you can later request, for up to 2 years from the end of your participation in the study, that they not be used for this research. To make this request, contact the study site and let them know that you now do not want your specimens to be used for research. Please understand that if the code identifying your specimens has been removed, we will not be able to find out which specimens are yours. In this case, they may still be used for research. Results from research that was done using your specimens before you changed your mind can still be used by the researchers. There is no end date for how long your specimens will be kept.

You agree that your leftover specimens may be used for other research purposes.

Please Initial.

_____*Yes, You agree* _____*No, you do not agree*

21 - Consent

Your signature below indicates your permission to take part in this research and to the use and disclosure of your protected health information:

Signature of Subject	Date
	Time
Printed Name of Subject	
Investigator Signature	Date
	Time
Printed Name of Investigator	
Signature of Witness to Signature	Date
	Time
Printed Name of Person Witnessing Signature	

My signature indicates that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

☐ ***Check box ONLY if the witness is an "impartial" witness*** *- an individual (greater than 18 years of age) with no affiliations to the patient (e.g. not a relative) and/or to the research study (e.g. not a study coordinator). An "impartial" witness is only required when a "short form" consent form is used or the subject is unable to read the consent form and the written informed consent document is read and comprehended by the subject or the subject's legally authorized representative and oral consent is given by either the subject or the subject's legally authorized representative.*

Signature of Witness to Signature	Date
	Time
Printed Name of Witness to Signature	