CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-GBM-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**119437**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-310-674-6711**
SAFETY FAX:	**1-310-826-6139**
ORIGINAL PROTOCOL:	**August 9, 2013**
AMENDMENT 1:	**November 12, 2013**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of ALDOXORUBICIN to subjects with unresectable glioblastoma (GBM) whose tumors have progressed following prior treatment with surgery, radiation and temozolomide, as measured by PFS according to the Response Assessment in Neuro-Oncology (RANO) Working Group Criteria (see Appendix F) and OS. **Secondary Objectives:** The secondary objectives of this study are to evaluate the safety of ALDOXORUBICIN in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiogram (ECHO) evaluations, electrocardiogram (ECG) results, weight, and the change in performance status as measured by the Karnofsky Performance Scale.	
Study Rationale and Significance: ALDOXORUBICIN is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with unresectable GBM who have failed prior surgery, radiation and chemotherapy with temozolomide regimens and bevacizumab have an extremely poor prognosis with progression-free survival (PFS) of around 8 weeks and median overall survival (OS) of approximately 8-16 weeks, depending on whether salvage therapy is administered. Recently, we have demonstrated in an orthotopic xenograft model of GBM in mice that ALDOXORUBICIN significantly retards the growth of the tumor and doubles the survival of animals when compared to treatment with either saline or doxorubicin. We have also shown that this molecule collects inside the tumor and not in normal brain parenchyma. Doxorubicin does not penetrate into either the tumor or the brain. Thus, ALDOXORUBICIN may be able to effectively treat patients with advanced GBM that have progressed after standard therapies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Design and Methodology:

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalent) intravenously on Day 1, every 21 days until evidence of tumor progression, unacceptable toxicity or withdrawal of consent. Subjects will be randomly assigned to either dose of ALDOXORUBICIN. G-CSF (Neupogen or Neulasta) should be administered as primary prophylaxis to all subjects according to the ASCO Guidelines (see Appendix E).

Tumor response (complete response [CR], partial response [PR] and stable disease [SD]) will be monitored at Screening, then every 6 weeks ± 5 days using the RANO Working Group Criteria (see Appendix F), and treatment will continue every 21 days until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Median PFS, PFS at 12 and 18 weeks, and 6 months, SD rate at 12 weeks, and OS will be monitored as other primary objectives. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, Karnofsky Performance Status (see Appendix B), documentation of corticosteroid usage and ECGs will be performed. Cardiac function will also be followed periodically using ECHOs.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed unresectable GBM. Subjects with recurrent disease whose prior pathology demonstrated GBM will not need to be re-biopsied. Subjects with prior low-grade glioma or anaplastic glioma are eligible if histological assessment demonstrates transformation into GBM.
3. Cancer progression after treatment with the following: surgery, radiation therapy and temozolomide with no other therapy prior to tumor recurrence.
    a. Radiographic progression by RANO Working Group Criteria (see Appendix F) will be confirmed by Imaging Endpoints, a central imaging vendor; or
    b. Confirmation by tumor biopsy if conducted within 4 weeks of Randomization.
4. An interval of at least 12 weeks after last dose of radiation and temozolomide is required, unless cancer progression is proven by diagnostic tumor biopsy.
5. Stable or decreasing dose of corticosteroids for at least 7 days prior to Randomization.
6. Capable of providing informed consent and complying with trial procedures.
7. Karnofsky Performance Status (see Appendix B) ≥70.
8. Life expectancy ≥8 weeks.
9. Measurable tumor lesions according to RANO Working Group Criteria (see Appendix F).
    a. In the case that there is “non-measureable” disease due to a radical surgical resection prior to screening, the subject may still qualify if Inclusion #3(b) is met.
10. Women must not be able to become pregnant (e.g. post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
11. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
12. Geographic accessibility to the site, i.e. the ability to come to the study site for each scheduled appointment and evaluation.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to an anthracycline.
2. Any therapeutic regimen for treatment of recurrent tumor after first line treatment with surgery, radiation and temozolomide.
3. Prior treatment with bevacizumab or an experimental anti-angiogenic agent.
4. Palliative surgery and/or radiation treatment < 4 weeks prior to Randomization.
5. Exposure to any investigational agent within 30 days of Randomization.
6. History of other malignancies (except cured basal cell carcinoma, superficial bladder cancer or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥3 years.
7. Laboratory values: Screening serum creatinine >1.5× upper limit of normal (ULN), alanine aminotransferase (ALT) > 2.5×ULN, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <27% for females or <30% for males, serum albumin ≤2.5 g/dL, prothrombin time (PT)/international normalized ratio (INR) >1.5×ULN or >3×ULN.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

8. Evidence of central nervous system (CNS) hemorrhage Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 on baseline magnetic resonance imaging (MRI).
9. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (see Appendix D).
10. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix G).
11. Baseline QTc >470 msec and/or previous history of QT prolongation.
12. History or signs of active coronary artery disease with or without angina pectoris.
13. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.
14. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals, or anti-fungals.
15. History of HIV infection.
16. Major surgery, except diagnostic tumor biopsy, within 4 weeks prior to Randomization.
17. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
18. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 28 subjects will be enrolled (14 at each dose level) in 3-5 study centers in the US.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of ALDOXORUBICIN reconstituted by adding a sterile solution of 50:50 ethanol:water, administration completed within 2 hours (of being reconstituted) as a 30 minute IV infusion in Lactated Ringer's solution. Total doses of either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalents).

Reference Therapy, Dose and Mode of Administration:
None

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- OS
- Objective tumor response (RANO Working Group Criteria [see Appendix F])
- PFS at 12 and 18 weeks and 6 months
- SD rate at 12 weeks
- Karnofsky Performance Status (see Appendix B)
- Corticosteroid usage

Safety:
The following safety variables will be assessed over the course of the study:
- AEs
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, ECHO evaluations, ECG results and laboratory test results
- Use of concomitant medications

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses.

Efficacy:
Tumor response by MRI will be monitored every 6 weeks until disease progression. For the estimation of PFS and OS a Kaplan-Meier analysis will be performed. The percentage of subjects with CRs or PRs, or SD will be evaluated every 6 weeks.

Safety:
The safety data will be summarized for all subjects. Total number of AEs leading to withdrawal and abnormal laboratory tests will be evaluated. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, ECHO, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimen. Descriptive evaluation denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	All Other Cycles	Every 6 Weeks ± 5 Days from Cycle 1-Day 1	End of Study or Early Termination	Follow-up[12]
Signed Informed Consent	X					
Review Inclusion/Exclusion		X				
Medical History[1]	X					
Physical Examination	X	X	X		X	
Height (cm)	X					
Weight (kg)	X	X	X			
BSA Calculation[2]		X	X			
Vital Signs[3]	X	X	X		X	
Karnofsky Performance Status	X	X	X		X	
MRI scan / Tumor Assessments	X[4]			X[8]	X[8,13]	
ECG	X	X[15]	X[15]		X[13]	
ECHO (with ejection fraction)	X		X[11]		X[11]	
CBC w/differential & platelets[5]	X	X[14]	X		X	
Serum Chemistries[5,6]	X	X[14]	X		X	
Urinalysis[7]	X				X	
Serum/Urine Pregnancy Test	X					
ALDOXORUBICIN Administration		X	X			
Concomitant Medications[9]	X	X	X		X	
Adverse Events[10]		X	X		X	
Telephone Follow-Up						X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (see Section 6 for details).

1. To include concurrent baseline conditions (using NCI CTCAE, version 4.0 [published 28 May 2009] [see Appendix C]), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy, antibody therapy and radiotherapy).
2. BSA only needs to be calculated if there has been a change >10% in body weight from Cycle 1-Day 1.
3. Blood pressure, pulse, respiratory rate, and temperature. Vital signs will be monitored every 15 minutes starting immediately prior to ALDOXORUBICIN dosing and ending approximately 30 minutes after completion of infusion.
4. MRI scan of brain with contrast to document disease status. If scan was taken within 21 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed within 7 days of starting chemotherapy.
    a. Historical MRI scans no older than 2 months prior to screening must be electronically submitted to Imaging Endpoints to confirm radiographic progression.
    b. All scans must be electronically submitted to Imaging Endpoints. Please refer to your Imaging Manual for details.
    c. If a surgical resection was completed during the screening period and demonstrates disease progression, the MRI may show “non-measureable” disease and will be used to demonstrate disease progression only.
5. During treatment, if any drug-related and/or clinically significant toxicity occurs, retest frequently until stable or resolving and in accordance with GCP. **Note: CBC with differential and platelet count must be performed weekly during each cycle.**
6. To include BUN, phosphorus, magnesium, LDH, creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, ALP, AST, ALT, electrolytes (chloride, sodium, potassium, and bicarbonate), PT/INR (at screening only).
7. Lab urinalysis to include protein, specific gravity, glucose, and blood.
8. Tumor response must be monitored during treatment every 6 weeks ± 5 days from Cycle 1-Day 1 regardless of dosing delays. The final assessment to be done 3 weeks following final ALDOXORUBICIN administration.
9. To include all medications taken within 30 days prior to study Randomization.
10. Subject will be followed until resolution of any drug-related AE or SAE occurring during the study, including within 30 days of last administration of study medication, or when the subject begins alternative therapy; whichever is sooner.
11. Cycle 4 and End of Treatment visit if later than Cycle 4. Additional testing can be done if clinically indicated.
12. Follow-up by telephone will be conducted in all subjects every 8 weeks to determine date of death.
13. If not done within last 14 days.
14. No need to repeat if performed within 21 days of Randomization.
15. ECGs will be performed pre-dose and at 1 hour post-dose (the anticipated maximal concentration).

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-GBM-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**119437**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-310-674-6711**
SAFETY FAX:	**1-310-826-6139**
ORIGINAL PROTOCOL:	**August 9, 2013**
AMENDMENT 1:	**November 12, 2013**
AMENDMENT 2:	**February 4, 2014**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide	
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Study Rationale and Significance: ALDOXORUBICIN is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with unresectable GBM who have failed prior surgery, radiation and chemotherapy with temozolomide regimens and bevacizumab have an extremely poor prognosis with progression-free survival (PFS) of around 8 weeks and median overall survival (OS) of approximately 8-16 weeks, depending on whether salvage therapy is administered. Recently, we have demonstrated in an orthotopic xenograft model of GBM in mice that ALDOXORUBICIN significantly retards the growth of the tumor and doubles the survival of animals when compared to treatment with either saline or doxorubicin. We have also shown that this molecule collects inside the tumor and not in normal brain parenchyma. Doxorubicin does not penetrate into either the tumor or the brain. Thus, ALDOXORUBICIN may be able to effectively treat patients with advanced GBM that have progressed after standard therapies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Design and Methodology:

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalent) intravenously on Day 1, every 21 days until evidence of tumor progression, unacceptable toxicity or withdrawal of consent. Subjects will be randomly assigned to either dose of ALDOXORUBICIN. G-CSF (Neupogen or Neulasta) should be administered as primary prophylaxis to all subjects according to the ASCO Guidelines (see Appendix E).

Tumor response (complete response [CR], partial response [PR] and stable disease [SD]) will be monitored at Screening, then every 6 weeks ± 5 days using the RANO Working Group Criteria (see Appendix F), and treatment will continue every 21 days until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Median PFS, PFS at 12 and 18 weeks, and 6 months, SD rate at 12 weeks, and OS will be monitored as other primary objectives. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, Karnofsky Performance Status (see Appendix B), documentation of corticosteroid usage and ECGs will be performed. Cardiac function will also be followed periodically using ECHOs.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed unresectable GBM. Subjects with recurrent disease whose prior pathology demonstrated GBM will not need to be re-biopsied. Subjects with prior low-grade glioma or anaplastic glioma are eligible if histological assessment demonstrates transformation into GBM.
3. Cancer progression after treatment with the following: surgery, radiation therapy and temozolomide with no other therapy prior to tumor recurrence.
    a. Radiographic progression by RANO Working Group Criteria (see Appendix F) will be confirmed by Imaging Endpoints, a central imaging vendor; or
    b. Confirmation by tumor biopsy if conducted within 4 weeks of Randomization.
4. An interval of at least 12 weeks after last dose of radiation and temozolomide is required, unless cancer progression is proven by diagnostic tumor biopsy. If temozolomide is being used in a maintenance phase, there must be a 28-day washout period prior to Randomization.
5. Stable or decreasing dose of corticosteroids for at least 7 days prior to Randomization.
6. Capable of providing informed consent and complying with trial procedures.
7. Karnofsky Performance Status (see Appendix B) ≥70.
8. Life expectancy ≥8 weeks.
9. Measurable tumor lesions according to RANO Working Group Criteria (see Appendix F).
    a. In the case that there is “non-measureable” disease due to a radical surgical resection prior to screening, the subject may still qualify if Inclusion #3(b) is met.
10. Women must not be able to become pregnant (e.g. post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
11. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
12. Geographic accessibility to the site, i.e. the ability to come to the study site for each scheduled appointment and evaluation.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to an anthracycline.
2. Any therapeutic regimen for treatment of recurrent tumor after first line treatment with surgery, radiation and temozolomide.
3. Prior treatment with bevacizumab or an experimental anti-angiogenic agent.
4. Palliative surgery and/or radiation treatment < 4 weeks prior to Randomization.
5. Exposure to any investigational agent within 30 days of Randomization.
6. History of other malignancies (except cured basal cell carcinoma, superficial bladder cancer or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥3 years.
7. Laboratory values: Screening serum creatinine >1.5× upper limit of normal (ULN), alanine aminotransferase (ALT) > 2.5×ULN, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <27% for females or <30% for males, serum albumin ≤2.5 g/dL, prothrombin time (PT)/ international normalized ratio (INR) >1.5×ULN or >3×ULN on anticoagulant with no evidence of active bleeding.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

8. Evidence of central nervous system (CNS) hemorrhage Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 on baseline magnetic resonance imaging (MRI).
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10. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix G).
11. Baseline QTc >470 msec and/or previous history of QT prolongation.
12. History or signs of active coronary artery disease with or without angina pectoris.
13. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.
14. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals, or anti-fungals.
15. History of HIV infection.
16. Major surgery, except diagnostic tumor biopsy, within 4 weeks prior to Randomization.
17. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
18. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 28 subjects will be enrolled (14 at each dose level) in 3-5 study centers in the US.

Test Product, Dose and Mode of Administration:
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Reference Therapy, Dose and Mode of Administration:
None

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- OS
- Objective tumor response (RANO Working Group Criteria [see Appendix F])
- PFS at 12 and 18 weeks and 6 months
- SD rate at 12 weeks
- Karnofsky Performance Status (see Appendix B)
- Corticosteroid usage

Safety:
The following safety variables will be assessed over the course of the study:
- AEs
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, ECHO evaluations, ECG results and laboratory test results
- Use of concomitant medications

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses.

Efficacy:
Tumor response by MRI will be monitored every 6 weeks until disease progression. For the estimation of PFS and OS a Kaplan-Meier analysis will be performed. The percentage of subjects with CRs or PRs, or SD will be evaluated every 6 weeks.

Safety:
The safety data will be summarized for all subjects. Total number of AEs leading to withdrawal and abnormal laboratory tests will be evaluated. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, ECHO, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimen. Descriptive evaluation denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	All Other Cycles	Every 6 Weeks ± 5 Days from Cycle 1-Day 1	End of Study or Early Termination	Follow-up[12]
Signed Informed Consent	X					
Review Inclusion/Exclusion		X				
Medical History[1]	X					
Physical Examination	X	X	X		X	
Height (cm)	X					
Weight (kg)	X	X	X			
BSA Calculation[2]		X	X			
Vital Signs[3]	X	X	X		X	
Karnofsky Performance Status	X	X	X		X	
MRI scan / Tumor Assessments	X[4]			X[8]	X[8,13]	
ECG	X	X[15]	X[15]		X[13]	
ECHO (with ejection fraction)	X		X[11]		X[11]	
CBC w/differential & platelets[5]	X	X[14]	X		X	
Serum Chemistries[5,6]	X	X[14]	X		X	
Urinalysis[7]	X				X	
Serum/Urine Pregnancy Test	X					
ALDOXORUBICIN Administration		X	X			
Concomitant Medications[9]	X	X	X		X	
Adverse Events[10]		X	X		X	
Telephone Follow-Up						X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (see Section 6 for details).

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-GBM-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**119437**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
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ORIGINAL PROTOCOL:	**August 9, 2013**
AMENDMENT 1:	**November 12, 2013**
AMENDMENT 2:	**February 4, 2014**
AMENDMENT 3:	**September 10, 2014**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of ALDOXORUBICIN to subjects with unresectable glioblastoma (GBM) whose tumors have progressed following prior treatment with surgery, radiation and temozolomide, as measured by PFS according to the Response Assessment in Neuro-Oncology (RANO) Working Group Criteria (see Appendix F) and OS. **Secondary Objectives:** The secondary objectives of this study are to evaluate the safety of ALDOXORUBICIN in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiogram (ECHO) evaluations, electrocardiogram (ECG) results, weight, and the change in performance status as measured by the Karnofsky Performance Scale.	
Study Rationale and Significance: ALDOXORUBICIN is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with unresectable GBM who have failed prior surgery, radiation and chemotherapy with temozolomide regimens and bevacizumab have an extremely poor prognosis with progression-free survival (PFS) of around 8 weeks and median overall survival (OS) of approximately 8-16 weeks, depending on whether salvage therapy is administered. Recently, we have demonstrated in an orthotopic xenograft model of GBM in mice that ALDOXORUBICIN significantly retards the growth of the tumor and doubles the survival of animals when compared to treatment with either saline or doxorubicin. We have also shown that this molecule collects inside the tumor and not in normal brain parenchyma. Doxorubicin does not penetrate into either the tumor or the brain. Thus, ALDOXORUBICIN may be able to effectively treat patients with advanced GBM that have progressed after standard therapies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Design and Methodology:

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalent) intravenously on Day 1, every 21 days until evidence of tumor progression, unacceptable toxicity or withdrawal of consent. Subjects will be randomly assigned to either dose of ALDOXORUBICIN. G-CSF (Neupogen or Neulasta) should be administered as primary prophylaxis to all subjects according to the ASCO Guidelines (see Appendix E).

Tumor response (complete response [CR], partial response [PR] and stable disease [SD]) will be monitored at Screening, then every 6 weeks ± 5 days using the RANO Working Group Criteria (see Appendix F), and treatment will continue every 21 days until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Median PFS, PFS at 12 and 18 weeks, and 6 months, SD rate at 12 weeks, and OS will be monitored as other primary objectives. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, Karnofsky Performance Status (see Appendix B), documentation of corticosteroid usage and ECGs will be performed. Cardiac function will also be followed periodically using ECHOs.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed unresectable GBM. Subjects with recurrent disease whose prior pathology demonstrated GBM will not need to be re-biopsied. Subjects with prior low-grade glioma or anaplastic glioma are eligible if histological assessment demonstrates transformation into GBM.
3. Cancer progression after treatment with the following: surgery, radiation therapy and temozolomide with no other therapy prior to tumor recurrence.
    a. Radiographic progression by RANO Working Group Criteria (see Appendix F) will be confirmed by Imaging Endpoints, a central imaging vendor; or
    b. Confirmation by tumor biopsy if conducted within 4 weeks of Randomization.
4. An interval of at least 12 weeks after last dose of radiation and temozolomide is required, unless cancer progression is proven by diagnostic tumor biopsy. If temozolomide is being used in a maintenance phase, there must be a 28-day washout period prior to Randomization.
5. Stable or decreasing dose of corticosteroids for at least 7 days prior to Randomization.
6. Capable of providing informed consent and complying with trial procedures.
7. Karnofsky Performance Status (see Appendix B) ≥70.
8. Life expectancy ≥8 weeks.
9. Measurable tumor lesions according to RANO Working Group Criteria (see Appendix F).
    a. In the case that there is “non-measureable” disease due to a radical surgical resection prior to screening, the subject may still qualify if Inclusion #3(b) is met.
10. Women must not be able to become pregnant (e.g. post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
11. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
12. Geographic accessibility to the site, i.e. the ability to come to the study site for each scheduled appointment and evaluation.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to an anthracycline.
2. Any therapeutic regimen for treatment of recurrent tumor after first line treatment with surgery, radiation and temozolomide.
3. Prior treatment with bevacizumab or an experimental anti-angiogenic agent.
4. Palliative surgery and/or radiation treatment < 4 weeks prior to Randomization.
5. Exposure to any investigational agent within 30 days of Randomization.
6. History of other malignancies (except cured basal cell carcinoma, superficial bladder cancer or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥3 years.
7. Laboratory values: Screening serum creatinine >1.5× upper limit of normal (ULN), alanine aminotransferase (ALT) > 2.5×ULN, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <27% for females or <30% for males, serum albumin ≤2.5 g/dL, prothrombin time (PT)/ international normalized ratio (INR) >1.5×ULN or >3×ULN on anticoagulant with no evidence of active bleeding.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

8. Evidence of central nervous system (CNS) hemorrhage Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 on baseline magnetic resonance imaging (MRI).
9. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (see Appendix D).
10. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix G).
11. Baseline QTc >470 msec and/or previous history of QT prolongation.
12. History or signs of active coronary artery disease with or without angina pectoris.
13. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.
14. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals, or anti-fungals.
15. History of HIV infection.
16. Major surgery, except diagnostic tumor biopsy, within 4 weeks prior to Randomization.
17. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
18. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 28 subjects will be enrolled (14 at each dose level) in 3-5 study centers in the US.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of ALDOXORUBICIN reconstituted by adding a sterile solution of 50:50 ethanol:water, administration completed within 2 hours (of being reconstituted) as a 30 minute IV infusion in Lactated Ringer's solution. Total doses of either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalents).

Reference Therapy, Dose and Mode of Administration:
None

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- OS
- Objective tumor response (RANO Working Group Criteria [see Appendix F])
- PFS at 12 and 18 weeks and 6 months
- SD rate at 12 weeks
- Karnofsky Performance Status (see Appendix B)
- Corticosteroid usage

Safety:
The following safety variables will be assessed over the course of the study:
- AEs
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, ECHO evaluations, ECG results and laboratory test results
- Use of concomitant medications

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses.

Efficacy:
Tumor response by MRI will be monitored every 6 weeks until disease progression. For the estimation of PFS and OS a Kaplan-Meier analysis will be performed. The percentage of subjects with CRs or PRs, or SD will be evaluated every 6 weeks.

Safety:
The safety data will be summarized for all subjects. Total number of AEs leading to withdrawal and abnormal laboratory tests will be evaluated. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, ECHO, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimen. Descriptive evaluation denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	All Other Cycles	Every 6 Weeks ± 5 Days from Cycle 1-Day 1	End of Study or Early Termination	Follow-up[12]
Signed Informed Consent	X					
Review Inclusion/Exclusion		X				
Medical History[1]	X					
Physical Examination	X	X	X		X	
Height (cm)	X					
Weight (kg)	X	X	X			
BSA Calculation[2]		X	X			
Vital Signs[3]	X	X	X		X	
Karnofsky Performance Status	X	X	X		X	
MRI scan / Tumor Assessments	X[4]			X[8]	X[8,13]	
ECG	X	X[15]	X[15]		X[13]	
ECHO (with ejection fraction)	X		X[11]		X[11]	
CBC w/differential & platelets[5]	X	X[14]	X		X	
Serum Chemistries[5,6]	X	X[14]	X		X	
Urinalysis[7]	X				X	
Serum/Urine Pregnancy Test	X					
ALDOXORUBICIN Administration		X	X			
Concomitant Medications[9]	X	X	X		X	
Adverse Events[10]		X	X		X	
Telephone Follow-Up						X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (see Section 6 for details).

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-GBM-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**119437**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-310-674-6711**
SAFETY FAX:	**1-310-826-6139**
ORIGINAL PROTOCOL:	**August 9, 2013**
AMENDMENT 1:	**November 12, 2013**
AMENDMENT 2:	**February 4, 2014**
AMENDMENT 3:	**September 10, 2014**
AMENDMENT 4:	**January 14, 2015**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of ALDOXORUBICIN to subjects with unresectable glioblastoma (GBM) whose tumors have progressed following prior treatment with surgery, radiation and temozolomide, as measured by PFS according to the Response Assessment in Neuro-Oncology (RANO) Working Group Criteria (see Appendix F) and OS. **Secondary Objectives:** The secondary objectives of this study are to evaluate the safety of ALDOXORUBICIN in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiogram (ECHO) evaluations, electrocardiogram (ECG) results, weight, and the change in performance status as measured by the Karnofsky Performance Scale.	
Study Rationale and Significance: ALDOXORUBICIN is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with unresectable GBM who have failed prior surgery, radiation and chemotherapy with temozolomide regimens and bevacizumab have an extremely poor prognosis with progression-free survival (PFS) of around 8 weeks and median overall survival (OS) of approximately 8-16 weeks, depending on whether salvage therapy is administered. Recently, we have demonstrated in an orthotopic xenograft model of GBM in mice that ALDOXORUBICIN significantly retards the growth of the tumor and doubles the survival of animals when compared to treatment with either saline or doxorubicin. We have also shown that this molecule collects inside the tumor and not in normal brain parenchyma. Doxorubicin does not penetrate into either the tumor or the brain. Thus, ALDOXORUBICIN may be able to effectively treat patients with advanced GBM that have progressed after standard therapies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Design and Methodology:

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalent) intravenously on Day 1, every 21 days until evidence of tumor progression, unacceptable toxicity or withdrawal of consent. Subjects will be randomly assigned to either dose of ALDOXORUBICIN. G-CSF (Neupogen or Neulasta) should be administered as primary prophylaxis to all subjects according to the ASCO Guidelines (see Appendix E). **Note: ALDOXORUBICIN, at higher doses, has been associated with >20% incidence of grade 3 or 4 neutropenia. Therefore, the administration of G-CSF should occur even during Cycle 1 for subjects receiving the 350 mg/m^2 dose of ALDOXORUBICIN.**

Tumor response (complete response [CR], partial response [PR] and stable disease [SD]) will be monitored at Screening, then every 6 weeks (±5 days) using the RANO Working Group Criteria (see Appendix F), and treatment will continue every 21 days until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Median PFS, PFS at 12 and 18 weeks, and 6 months, SD rate at 12 weeks, and OS will be monitored as other primary objectives. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry and complete blood count [CBC]), vital signs, weight measurements, Karnofsky Performance Status (see Appendix B), documentation of corticosteroid usage and ECGs will be performed. All subjects will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically using ECHOs.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed unresectable GBM. Subjects with recurrent disease whose prior pathology demonstrated GBM will not need to be re-biopsied. Subjects with prior low-grade glioma or anaplastic glioma are eligible if histological assessment demonstrates transformation into GBM.
3. Cancer progression after treatment with the following: surgery, radiation therapy and temozolomide with no other therapy prior to tumor recurrence.
    a. Radiographic progression by RANO Working Group Criteria (see Appendix F) will be confirmed by Imaging Endpoints, a central imaging vendor; or
    b. Confirmation by tumor biopsy if conducted within 4 weeks of Randomization.
4. An interval of at least 12 weeks after last dose of radiation and temozolomide is required, unless cancer progression is proven by diagnostic tumor biopsy. If temozolomide is being used in a maintenance phase, there must be a 28-day washout period prior to Randomization.
5. Stable or decreasing dose of corticosteroids for at least 7 days prior to Randomization.
6. Capable of providing informed consent and complying with trial procedures.
7. Karnofsky Performance Status (see Appendix B) ≥70.
8. Life expectancy ≥8 weeks.
9. Measurable tumor lesions according to RANO Working Group Criteria (see Appendix F).
    a. In the case that there is “non-measureable” disease due to a radical surgical resection prior to screening, the subject may still qualify if Inclusion #3(b) is met.
10. Women must not be able to become pregnant (e.g. post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
11. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
12. Geographic accessibility to the site, i.e. the ability to come to the study site for each scheduled appointment and evaluation.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to an anthracycline.
2. Any therapeutic regimen for treatment of recurrent tumor after first line treatment with surgery, radiation and temozolomide.
3. Prior treatment with bevacizumab or an experimental anti-angiogenic agent.
4. Palliative surgery and/or radiation treatment < 4 weeks prior to Randomization.
5. Exposure to any investigational agent within 30 days of Randomization.
6. History of other malignancies (except cured basal cell carcinoma, superficial bladder cancer or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥3 years.
7. Laboratory values: Screening serum creatinine >1.5× upper limit of normal (ULN), alanine aminotransferase (ALT) > 2.5×ULN, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <27% for females or <30% for males, serum albumin ≤2.5 g/dL, prothrombin time (PT)/ international normalized ratio (INR) >1.5×ULN or >3×ULN on anticoagulant with no evidence of active bleeding.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

8. Anion gap > 16 meq/L or arterial blood pH < 7.30.
9. Evidence of central nervous system (CNS) hemorrhage Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 on baseline magnetic resonance imaging (MRI).
10. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (see Appendix D).
11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix G).
12. Baseline QTc >470 msec and/or previous history of QT prolongation.
13. History or signs of active coronary artery disease with or without angina pectoris.
14. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.
15. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals, or anti-fungals.
16. History of HIV infection.
17. Major surgery, except diagnostic tumor biopsy, within 4 weeks prior to Randomization.
18. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
19. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 28 subjects will be enrolled (14 at each dose level) in 3-5 study centers in the US.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of ALDOXORUBICIN reconstituted by adding a sterile solution of 50:50 ethanol:water, administration completed within 2 hours (of being reconstituted) as a 30 minute IV infusion in Lactated Ringer's solution. Total doses of either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalents).

Reference Therapy, Dose and Mode of Administration:
None

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- OS
- Objective tumor response (RANO Working Group Criteria [see Appendix F])
- PFS at 12 and 18 weeks and 6 months
- SD rate at 12 weeks
- Pseudo progression events on DSC-MRI in subjects who undergo additional MRI sequence evaluation
- Karnofsky Performance Status (see Appendix B)
- Corticosteroid usage

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Safety:

The following safety variables will be assessed over the course of the study:

- AEs
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, ECHO evaluations, ECG results and laboratory test results
- Use of concomitant medications

Statistical Methods:

In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses.

Efficacy:

Tumor response by MRI will be monitored every 6 weeks (±5 days) until disease progression. For the estimation of PFS and OS a Kaplan-Meier analysis will be performed. The percentage of subjects with CRs or PRs, or SD will be evaluated every 6 weeks.

Safety:

The safety data will be summarized for all subjects. Total number of AEs leading to withdrawal and abnormal laboratory tests will be evaluated. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, ECHO, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimen. Descriptive evaluation denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	All Other Cycles	Every 6 Weeks ± 5 Days from Cycle 1-Day 1	End of Study or Early Termination	Follow-up[12]
Signed Informed Consent	X					
Review Inclusion/Exclusion		X				
Medical History[1]	X					
Physical Examination	X	X	X		X	
Height (cm)	X					
Weight (kg)	X	X	X			
BSA Calculation[2]		X	X			
Vital Signs[3]	X	X	X		X	
Karnofsky Performance Status	X	X	X		X	
MRI scan / Tumor Assessments	X[4]			X[8]	X[8,13]	
ECG	X	X[15]	X[15]		X[13]	
ECHO (with ejection fraction)	X		X[11]		X[11]	
CBC w/differential & platelets[5]	X	X[14]	X		X	
Serum Chemistries[5,6]	X*	X[14]	X		X	
Urinalysis[7]	X				X	
Serum/Urine Pregnancy Test	X					
ALDOXORUBICIN Administration		X	X			
Concomitant Medications[9]	X	X	X		X	
Adverse Events[10]		X	X		X	
Telephone Follow-Up						X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (see Section 6 for details).

*Arterial blood gas test, if needed, to confirm acid levels.

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Multiforme Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-GBM-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**TBD**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-310-674-6711**
SAFETY FAX:	**1-310-826-6139**
DATE OF PROTOCOL:	**August 9, 2013**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Aldoxorubicin in Subjects with Unresectable Glioblastoma Multiforme Whose Tumors Have Progressed Following Prior Treatment with Surgery, Radiation and Temozolomide	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of ALDOXORUBICIN to subjects with unresectable glioblastoma multiforme (GBM) whose tumors have progressed following prior treatment with surgery, radiation and temozolomide. **Secondary Objectives:** The secondary objectives of this study are to evaluate the safety of ALDOXORUBICIN in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiogram (ECHO) evaluations, electrocardiogram (ECG) results, and weight, and the change in performance status as measured by the Karnofsky Performance Scale.	
Study Rationale and Significance: ALDOXORUBICIN is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with unresectable GBM who have failed prior surgery, radiation and chemotherapy with temozolomide regimens and bevacizumab have an extremely poor prognosis with progression-free survival (PFS) of around 8 weeks and median overall survival (OS) of approximately 8-16 weeks, depending on whether salvage therapy is administered. Recently, we have demonstrated in an orthotopic xenograft model of GBM in mice that ALDOXORUBICIN significantly retards the growth of the tumor and doubles the survival of animals when compared to treatment with either saline or doxorubicin. We have also shown that this molecule collects inside the tumor and not in normal brain parenchyma. Doxorubicin does not penetrate into either the tumor or the brain. Thus, ALDOXORUBICIN may be able to effectively treat patients with advanced GBM that have progressed after standard therapies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Design and Methodology:

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalent) intravenously on Day 1, every 21 days until evidence of tumor progression, unacceptable toxicity or withdrawal of consent. Subjects will be randomly assigned to either dose of ALDOXORUBICIN. G-CSF (Neupogen or Neulasta) should be administered prophylactically according to the ASCO Guidelines (see Appendix E).

Tumor response (complete, partial response [PR] and stable disease [SD]) will be monitored at Screening, then every 6 weeks using the Response Assessment in Neuro-Oncology (RANO) Working Group Criteria (see Appendix F), and treatment will continue every 21 days until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Median PFS, PFS at 12 and 18 weeks, SD rate at 12 weeks, and OS will be monitored as other primary objectives. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, Karnofsky Performance Status (see Appendix B), corticosteroid usage and ECGs will be performed. Cardiac function will also be followed periodically using ECHOs.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-GBM-01	**Phase of Development:** 2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed unresectable GBM. Subjects with recurrent disease whose prior pathology demonstrated GBM will not need to be re-biopsied. Subjects with prior low-grade glioma or anaplastic glioma are eligible if histological assessment demonstrates transformation into GBM.
3. Cancer progression after treatment with the following: surgery, radiation therapy and temozolomide as first line treatment.
4. An interval of at least 4 weeks after last dose of radiation and temozolomide is required.
5. Stable or decreasing dose of corticosteroids for at least 7 days prior to enrollment.
6. Capable of providing informed consent and complying with trial procedures.
7. Karnofsky Performance Status (see Appendix B) ≥70.
8. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
9. Life expectancy ≥8 weeks.
10. Measurable tumor lesions according to RANO Working Group Criteria (see Appendix F).
11. Women must not be able to become pregnant (e.g. post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
12. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
13. Geographic accessibility to the site.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to an anthracycline.
2. Prior treatment with bevacizumab or an experimental anti-angiogenic agent.
3. Palliative surgery and/or radiation treatment < 4 weeks prior to Randomization.
4. Exposure to any investigational agent within 30 days of Randomization.
5. History of other malignancies (except cured basal cell carcinoma, superficial bladder cancer or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥3 years.
6. Laboratory values: Screening serum creatinine >1.5× upper limit of normal (ULN), alanine aminotransferase (ALT) > 2.5×ULN, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <27% for females or <30% for males, serum albumin ≤2.5 g/dL.
7. Evidence of central nervous system (CNS) hemorrhage Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 on baseline magnetic resonance imaging (MRI).
8. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (see Appendix D).
9. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
10. History or signs of active coronary artery disease with or without angina pectoris.
11. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.

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12. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals, or anti-fungals.
13. History of HIV infection.
14. Major surgery within 4 weeks prior to Randomization.
15. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
16. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 28 subjects will be enrolled (14 at each dose level) in 3-5 study centers in the US.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of ALDOXORUBICIN reconstituted by adding a sterile solution of 50/50 ethanol:water, administration completed within 2 hours (of being reconstituted) as a 30 minute IV infusion in Lactated Ringer's solution. Total doses of either 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) or 250 mg/m^2 (185 mg/m^2 doxorubicin equivalents).

Reference Therapy, Dose and Mode of Administration:
None

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- OS
- Objective tumor response (RANO Working Group Criteria [see Appendix F])
- PFS at 12 and 18 weeks
- SD rate at 12 weeks
- Karnofsky Performance Status (see Appendix B)
- Corticosteroid usage

Safety:
The following safety variables will be assessed over the course of the study:
- AEs
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, ECHO evaluations, ECG results and laboratory test results
- Use of concomitant medications

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Statistical Methods:

In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses.

Efficacy:

Tumor response by MRI will be monitored every 6 weeks until disease progression. For the estimation of PFS and OS a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or PRs, or SD will be evaluated every 6 weeks.

Safety:

The safety data will be summarized for all subjects. Total number of AEs leading to withdrawal and abnormal laboratory tests will be evaluated. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, ECHO, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimen. Descriptive evaluation denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	All other cycles	Every other cycle	End of Study or Early Termination	Follow-up[12]
Signed informed consent	X					
Review inclusion/exclusion		X				
Medical history[1]	X					
Physical examination	X	X	X		X	
Height (cm)	X					
Weight (kg)	X	X	X			
BSA calculation[2]		X	X			
Vital signs[3]	X	X	X		X	
Karnofsky Performance Status	X	X	X		X	
MRI scan / tumor assesments	X[4]			X[8]	X[13]	
ECG	X	X	X		X	
ECHO (with ejection fraction)	X		X[11]		X[11]	
CBC w/differential & plts[5]	X	X	X		X	
Serum chemistries[5,6]	X	X[14]	X		X	
Urinalysis[7]	X				X	
Serum/urine pregnancy test	X					
ALDOXORUBICIN administration		X	X			
Concomitant medications[9]	X	X	X		X	
Adverse events[10]		X	X		X	
Telephone follow-up						X

NOTE: All assessments must be performed within 72 hour of each specified time parameter, except Cycle 1 (see Section 6 for details).