

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

CONFIDENTIAL

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SYNOPSIS

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

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/m² (260 mg/m² doxorubicin equivalent) or 250 mg/m² (185 mg/m² 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.

	otocol Number: DOXORUBICIN-P2-GBM-01	Phase of Development: 2
Stu	udy Population and Main Criter	ia for Inclusion/Exclusion:
	lusion Criteria:	
Sul	bjects must meet the following cr	iteria to be included in the study:
1.	Age ≥18 years of age; male or fe	male.
2.	Histologically or cytologically con prior pathology demonstrated GB	firmed unresectable GBM. Subjects with recurrent disease whose BM will not need to be re-biopsied. Subjects with prior low-grade eligible if histological assessment demonstrates transformation into
3.	Cancer progression after treatme with no other therapy prior to turn	ent with the following: surgery, radiation therapy and temozolomide nor recurrence.
	confirmed by Imaging E	on by RANO Working Group Criteria (see Appendix F) will be indpoints, a central imaging vendor; or piopsy if conducted within 4 weeks of Randomization.
4.	An interval of at least 12 weeks a cancer progression is proven by	Ifter last dose of radiation and temozolomide is required, unless diagnostic tumor biopsy.
5.	Stable or decreasing dose of cort	ticosteroids for at least 7 days prior to Randomization.
6.	Capable of providing informed co	onsent and complying with trial procedures.
7.	Karnofsky Performance Status (s	see Appendix B) ≥70.
8.	Life expectancy ≥8 weeks.	
9.		ling to RANO Working Group Criteria (see Appendix F).
	to screening, the subject	"non-measureable" disease due to a radical surgical resection prior t may still qualify if Inclusion #3(b) is met.
10.	sterile, or practicing adequate bir contraception includes: oral contr	th control methods) for the duration of the study. (Adequate raception, implanted contraception, intrauterine device implanted for nod in conjunction with spermicide.)
11.	Women of child bearing potential Visit and be non-lactating.	must have a negative serum or urine pregnancy test at the Screening
12.	Geographic accessibility to the si appointment and evaluation.	te, i.e. the ability to come to the study site for each scheduled
	clusion Criteria: ojects meeting the following criteria	a will not be enrolled:
1.	Prior exposure to an anthracyclin	
2.		ment of recurrent tumor after first line treatment with surgery,
3.		o or an experimental anti-angiogenic agent.
4.		n treatment < 4 weeks prior to Randomization.
5.	• ,	igent within 30 days of Randomization.
6.	History of other malignancies (ex	cept cured basal cell carcinoma, superficial bladder cancer or nless documented free of cancer for ≥3 years.
7.	Laboratory values: Screening ser aminotransferase (ALT) > 2.5×UI <1,500/mm ³ , platelet concentration level <27% for females or <30%	rum creatinine >1.5× upper limit of normal (ULN), alanine LN, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) on <100,000/mm ³ , absolute lymphocyte count <1000/mm ³ , hematocri for males, serum albumin ≤2.5 g/dL, prothrombin time o (INR) >1.5×ULN or >3×ULN.

Protocol Number: ALDOXORUBICIN-P2-GBM-	Phase of Development: 2 01
	bus system (CNS) hemorrhage Common Terminology Criteria for) ≥ grade 2 on baseline magnetic resonance imaging (MRI).
	tive heart failure (CHF) > class II of the New York Heart Association
10. Current, serious, clinically	y significant cardiac arrhythmias, defined as the existence of an absolute arrhythmias classified as Lown III, IV or V (Appendix G).
2	and/or previous history of QT prolongation.
	coronary artery disease with or without angina pectoris.
13. Serious myocardial dysfu	nction defined as ultrasound-determined absolute left ventricular 45% of predicted institutional normal value.
-	nt serious infection requiring treatment with antibiotics, anti-virals, or
15. History of HIV infection.	
•	gnostic tumor biopsy, within 4 weeks prior to Randomization.
, , ,	interfere with the subject's participation in the study or in the evaluation
18. Any condition that is unst	able and could jeopardize the subject's participation in the study.
Lyophilized powder in vials th	at contain 200 mg of ALDOXORUBICIN reconstituted by adding a
sterile solution of 50:50 ethar reconstituted) as a 30 minute	Nol:water, administration completed within 2 hours (of being IV infusion in Lactated Ringer's solution. Total doses of either ubicin equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents).
sterile solution of 50:50 ethar reconstituted) as a 30 minute 350 mg/m ² (260 mg/m ² doxor Reference Therapy, Dose a	nol:water, administration completed within 2 hours (of being IV) IV) IV infusion in Lactated Ringer's solution. Total doses of either
sterile solution of 50:50 ethar reconstituted) as a 30 minute 350 mg/m ² (260 mg/m ² doxor	nol:water, administration completed within 2 hours (of being IV infusion in Lactated Ringer's solution. Total doses of either ubicin equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents).
sterile solution of 50:50 ethar reconstituted) as a 30 minute 350 mg/m ² (260 mg/m ² doxor Reference Therapy, Dose a None Criteria for Evaluation: Efficacy: The following efficacy variable • PFS	nol:water, administration completed within 2 hours (of being IV infusion in Lactated Ringer's solution. Total doses of either ubicin equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents).
sterile solution of 50:50 ethar reconstituted) as a 30 minute 350 mg/m ² (260 mg/m ² doxor Reference Therapy, Dose a None Criteria for Evaluation: Efficacy: The following efficacy variabl • PFS • OS • Objective tumor response (• PFS at 12 and 18 weeks an	nol:water, administration completed within 2 hours (of being IV infusion in Lactated Ringer's solution. Total doses of either ubicin equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents). nd Mode of Administration: es will be evaluated as noted: RANO Working Group Criteria [see Appendix F])
sterile solution of 50:50 ethar reconstituted) as a 30 minute 350 mg/m ² (260 mg/m ² doxor Reference Therapy, Dose a None Criteria for Evaluation: Efficacy: The following efficacy variable • PFS • OS • Objective tumor response (• PFS at 12 and 18 weeks ar • SD rate at 12 weeks • Karnofsky Performance Sta • Corticosteroid usage	nol:water, administration completed within 2 hours (of being IV infusion in Lactated Ringer's solution. Total doses of either ubicin equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents). nd Mode of Administration: es will be evaluated as noted: RANO Working Group Criteria [see Appendix F]) nd 6 months
sterile solution of 50:50 ethar reconstituted) as a 30 minute 350 mg/m ² (260 mg/m ² doxor Reference Therapy, Dose a None Criteria for Evaluation: Efficacy: The following efficacy variable • PFS • OS • Objective tumor response (• PFS at 12 and 18 weeks ar • SD rate at 12 weeks • Karnofsky Performance Sta • Corticosteroid usage Safety:	nol:water, administration completed within 2 hours (of being IV infusion in Lactated Ringer's solution. Total doses of either ubicin equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents). nd Mode of Administration: es will be evaluated as noted: RANO Working Group Criteria [see Appendix F]) nd 6 months

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Protocol Number:

Phase of Development: 2

Statistical Methods:

ALDOXORUBICIN-P2-GBM-01

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.

	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	Х					
Review Inclusion/Exclusion		Х				
Medical History ¹	Х					
Physical Examination	Х	Х	Х		Х	
Height (cm)	Х					
Weight (kg)	Х	Х	Х			
BSA Calculation ²		Х	Х			
Vital Signs ³	Х	Х	Х		Х	
Karnofsky Performance Status	Х	Х	Х		Х	
MRI scan / Tumor Assessments	X ⁴			X ⁸	X ^{8,13}	
ECG	Х	X ¹⁵	X ¹⁵		X ¹³	
ECHO (with ejection fraction)	Х		X ¹¹		X ¹¹	
CBC w/differential & platelets ⁵	Х	X ¹⁴	Х		Х	
Serum Chemistries ^{5,6}	Х	X ¹⁴	Х		Х	
Urinalysis ⁷	Х				Х	
Serum/Urine Pregnancy Test	Х					
ALDOXORUBICIN Administration		Х	Х			
Concomitant Medications ⁹	Х	Х	Х		Х	
Adverse Events ¹⁰		Х	Х		Х	
Telephone Follow-Up						Х

APPENDIX A: Schedule of Treatment and Evaluations

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).
- 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.
- 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).



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PROTOCOL NUMBER: ALDOXORUBICIN-P2-GBM-01

STUDY DRUG: Aldoxorubicin

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ORIGINAL PROTOCOL: August 9, 2013

- AMENDMENT 1: November 12, 2013
- AMENDMENT 2: February 4, 2014

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SYNOPSIS

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

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.

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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.

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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.

	otocol Number: DOXORUBICIN-P2-GBM-01	Phase of Development: 2
Stu	dy Population and Main Criter	ia for Inclusion/Exclusion:
	lusion Criteria:	
		iteria to be included in the study:
1.	Age ≥18 years of age; male or fe	•
2.	Histologically or cytologically comprior pathology demonstrated GB	firmed unresectable GBM. Subjects with recurrent disease whose BM will not need to be re-biopsied. Subjects with prior low-grade ligible if histological assessment demonstrates transformation into
3.	Cancer progression after treatme with no other therapy prior to tum	ent with the following: surgery, radiation therapy and temozolomide or recurrence.
	confirmed by Imaging E	on by RANO Working Group Criteria (see Appendix F) will be indpoints, a central imaging vendor; or
л		biopsy if conducted within 4 weeks of Randomization. Ifter last dose of radiation and temozolomide is required, unless
4.	cancer progression is proven by o	diagnostic tumor biopsy. If temozolomide is being used in a been a 28-day washout period prior to Randomization.
5.	Stable or decreasing dose of cort	ticosteroids for at least 7 days prior to Randomization.
6.	Capable of providing informed co	nsent and complying with trial procedures.
7.	Karnofsky Performance Status (s	ee Appendix B) ≥70.
8.	Life expectancy ≥8 weeks.	
9.	Measurable tumor lesions accord	ling to RANO Working Group Criteria (see Appendix F).
		"non-measureable" disease due to a radical surgical resection prior t may still qualify if Inclusion #3(b) is met.
10.	sterile, or practicing adequate bir contraception includes: oral contr	th control methods) for the duration of the study. (Adequate raception, implanted contraception, intrauterine device implanted for nod in conjunction with spermicide.)
11.	Women of child bearing potential Visit and be non-lactating.	must have a negative serum or urine pregnancy test at the Screening
12.	Geographic accessibility to the sir appointment and evaluation.	te, i.e. the ability to come to the study site for each scheduled
	clusion Criteria: ojects meeting the following criteria	a will not be enrolled:
1.	Prior exposure to an anthracyclin	е.
2.	Any therapeutic regimen for treat radiation and temozolomide.	ment of recurrent tumor after first line treatment with surgery,
3.	Prior treatment with bevacizumat	o or an experimental anti-angiogenic agent.
4.	Palliative surgery and/or radiation	n treatment < 4 weeks prior to Randomization.
5.	Exposure to any investigational a	gent within 30 days of Randomization.
6.	carcinoma in situ of the cervix) ur	cept cured basal cell carcinoma, superficial bladder cancer or nless documented free of cancer for ≥3 years.
7.	aminotransferase (ALT) > 2.5×UL <1,500/mm ³ , platelet concentration hematocrit level <27% for female	rum creatinine >1.5× upper limit of normal (ULN), alanine _N, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) on <100,000/mm ³ , absolute lymphocyte count <1000/mm ³ , s or <30% for males, serum albumin \leq 2.5 g/dL, prothrombin time io (INR) >1.5×ULN or >3×ULN on anticoagulant with no evidence of

active bleeding.

Protocol Number: ALDOXORUBICIN-P2-GBM-01	Phase of Development: 2
	stem (CNS) hemorrhage Common Terminology Criteria for
· / -	de 2 on baseline magnetic resonance imaging (MRI). art failure (CHF) > class II of the New York Heart Association איר D)
10. Current, serious, clinically signif	ficant cardiac arrhythmias, defined as the existence of an absolute nmias classified as Lown III, IV or V (Appendix G).
	r previous history of QT prolongation.
	ary artery disease with or without angina pectoris.
	defined as ultrasound-determined absolute left ventricular of predicted institutional normal value.
14. Active, clinically significant serio anti-fungals.	ous infection requiring treatment with antibiotics, anti-virals, or
15. History of HIV infection.	
	c tumor biopsy, within 4 weeks prior to Randomization.
of the study results.	re with the subject's participation in the study or in the evaluation
18. Any condition that is unstable a	nd could jeopardize the subject's participation in the study.
• • •	4 at each dose level) in 3-5 study centers in the US.
sterile solution of 50:50 ethanol:wat reconstituted) as a 30 minute IV infu	tain 200 mg of ALDOXORUBICIN reconstituted by adding a er, administration completed within 2 hours (of being usion in Lactated Ringer's solution. Total doses of either equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents).
Reference Therapy, Dose and Mo None	de of Administration:
Criteria for Evaluation:	
Efficacy: The following efficacy variables will	be evaluated as noted:
PFS OS	
Objective tumor response (RANOPFS at 12 and 18 weeks and 6 m	Working Group Criteria [see Appendix F]) onths
 SD rate at 12 weeks Karnofsky Performance Status (se Corticosteroid usage 	ee Appendix B)
Safety:	
	e assessed over the course of the study:
	tment (tolerability)
 Ability to remain on assigned treat Clinical and laboratory data includ ECG results and laboratory test re Use of concomitant medications 	ling physical examinations, vital signs, weight, ECHO evaluations,

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Statistical Methods:

ALDOXORUBICIN-P2-GBM-01

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.

	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	Х					
Review Inclusion/Exclusion		Х				
Medical History ¹	Х					
Physical Examination	Х	Х	Х		Х	
Height (cm)	Х					
Weight (kg)	Х	Х	Х			
BSA Calculation ²		Х	Х			
Vital Signs ³	Х	Х	Х		Х	
Karnofsky Performance Status	Х	Х	Х		Х	
MRI scan / Tumor Assessments	X ⁴			X ⁸	X ^{8,13}	
ECG	Х	X ¹⁵	X ¹⁵		X ¹³	
ECHO (with ejection fraction)	Х		X ¹¹		X ¹¹	
CBC w/differential & platelets ⁵	Х	X ¹⁴	Х		Х	
Serum Chemistries ^{5,6}	Х	X ¹⁴	Х		Х	
Urinalysis ⁷	Х				Х	
Serum/Urine Pregnancy Test	Х					
ALDOXORUBICIN Administration	1	Х	Х			
Concomitant Medications ⁹	Х	Х	Х		Х	
Adverse Events ¹⁰		Х	Х		Х	
Telephone Follow-Up						Х

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



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AMENDMENT 3:

September 10, 2014

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SYNOPSIS

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ALDOXORUBICIN-P2-GBM-01	

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:

Phase of Development: 2

Study Design and Methodology:

ALDOXORUBICIN-P2-GBM-01

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at either 350 mg/m² (260 mg/m² doxorubicin equivalent) or 250 mg/m² (185 mg/m² 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.

	btocol Number: DOXORUBICIN-P2-GBM-01	Phase of Development: 2				
Stı	udy Population and Main Criter	ia for Inclusion/Exclusion:				
	lusion Criteria:					
	bjects must meet the following cri	-				
1. 2.	prior pathology demonstrated GB	nale. irmed unresectable GBM. Subjects with recurrent disease whose M will not need to be re-biopsied. Subjects with prior low-grade ligible if histological assessment demonstrates transformation into				
3.	Cancer progression after treatment with no other therapy prior to tume	nt with the following: surgery, radiation therapy and temozolomide or recurrence.				
	confirmed by Imaging E	on by RANO Working Group Criteria (see Appendix F) will be ndpoints, a central imaging vendor; or				
		iopsy if conducted within 4 weeks of Randomization.				
4.	cancer progression is proven by c	fter last dose of radiation and temozolomide is required, unless liagnostic tumor biopsy. If temozolomide is being used in a e a 28-day washout period prior to Randomization.				
5.						
6.		nsent and complying with trial procedures.				
7.	Karnofsky Performance Status (s	ee Appendix B) ≥70.				
8.	Life expectancy ≥8 weeks.					
9.		ing to RANO Working Group Criteria (see Appendix F).				
	to screening, the subjec	"non-measureable" disease due to a radical surgical resection prior t may still qualify if Inclusion #3(b) is met.				
10.	sterile, or practicing adequate birt contraception includes: oral contra	me pregnant (e.g. post-menopausal for at least 1 year, surgically h control methods) for the duration of the study. (Adequate aception, implanted contraception, intrauterine device implanted for od in conjunction with spermicide.)				
11.	Women of child bearing potential Visit and be non-lactating.	must have a negative serum or urine pregnancy test at the Screenin				
12.	Geographic accessibility to the sit appointment and evaluation.	e, i.e. the ability to come to the study site for each scheduled				
	clusion Criteria: bjects meeting the following criteria	will not be enrolled:				
1.	Prior exposure to an anthracycline	9.				
2.	Any therapeutic regimen for treatr radiation and temozolomide.	ment of recurrent tumor after first line treatment with surgery,				
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 ag	gent within 30 days of Randomization.				
6.	carcinoma in situ of the cervix) un	cept cured basal cell carcinoma, superficial bladder cancer or less documented free of cancer for ≥3 years.				
7.	aminotransferase (ALT) > 2.5×UL <1,500/mm ³ , platelet concentration hematocrit level <27% for females	um creatinine >1.5× upper limit of normal (ULN), alanine N, total bilirubin >1.5×ULN, absolute neutrophil count (ANC) on <100,000/mm ³ , absolute lymphocyte count <1000/mm ³ , s or <30% for males, serum albumin \leq 2.5 g/dL, prothrombin time o (INR) >1.5×ULN or >3×ULN on anticoagulant with no evidence of				

Protocol Number: ALDOXORUBICIN-P2-GBM-01	Phase of Development: 2
	stem (CNS) hemorrhage Common Terminology Criteria for
· · · ·	de 2 on baseline magnetic resonance imaging (MRI).
 Clinically evident congestive he (NYHA) guidelines (see Appendic) 	eart failure (CHF) > class II of the New York Heart Association
	ficant cardiac arrhythmias, defined as the existence of an absolute
	hmias classified as Lown III, IV or V (Appendix G).
11. Baseline QTc >470 msec and/c	or previous history of QT prolongation.
12. History or signs of active corona	ary artery disease with or without angina pectoris.
	defined as ultrasound-determined absolute left ventricular of predicted institutional normal value.
 Active, clinically significant serie anti-fungals. 	ous infection requiring treatment with antibiotics, anti-virals, or
15. History of HIV infection.	
	ic tumor biopsy, within 4 weeks prior to Randomization.
 Any condition that might interfe of the study results. 	re with the subject's participation in the study or in the evaluation
18. Any condition that is unstable a	nd could jeopardize the subject's participation in the study.
Jp to 28 subjects will be enrolled (1	14 at each dose level) in 3-5 study centers in the US.
Up to 28 subjects will be enrolled (1 Test Product, Dose and Mode of Lyophilized powder in vials that con sterile solution of 50:50 ethanol:wat reconstituted) as a 30 minute IV info	
Up to 28 subjects will be enrolled (1 Test Product, Dose and Mode of Lyophilized powder in vials that con sterile solution of 50:50 ethanol:wat reconstituted) as a 30 minute IV infr 350 mg/m ² (260 mg/m ² doxorubicin Reference Therapy, Dose and Mo	Administration: tain 200 mg of ALDOXORUBICIN reconstituted by adding a ter, administration completed within 2 hours (of being usion in Lactated Ringer's solution. Total doses of either equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents).
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Up to 28 subjects will be enrolled (1 Test Product, Dose and Mode of Lyophilized powder in vials that con- sterile solution of 50:50 ethanol:wat reconstituted) as a 30 minute IV info 350 mg/m ² (260 mg/m ² doxorubicin Reference Therapy, Dose and Mo None Criteria for Evaluation: Efficacy: The following efficacy variables will • PFS • OS • Objective tumor response (RANC • PFS at 12 and 18 weeks and 6 m • SD rate at 12 weeks • Karnofsky Performance Status (s • Corticosteroid usage Safety: The following safety variables will b • AEs • Ability to remain on assigned treat	Administration: htain 200 mg of ALDOXORUBICIN reconstituted by adding a ter, administration completed within 2 hours (of being usion in Lactated Ringer's solution. Total doses of either equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents). ode of Administration: be evaluated as noted: 0 Working Group Criteria [see Appendix F]) honths here Appendix B) here assessed over the course of the study: htment (tolerability) ding physical examinations, vital signs, weight, ECHO evaluations

Name of Sponsor/Company: CytRx Corporation
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Protocol Number:

Phase of Development: 2

Statistical Methods:

ALDOXORUBICIN-P2-GBM-01

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.

	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	Х					
Review Inclusion/Exclusion		Х				
Medical History ¹	Х					
Physical Examination	Х	Х	Х		Х	
Height (cm)	Х					
Weight (kg)	Х	Х	Х			
BSA Calculation ²		Х	Х			
Vital Signs ³	Х	Х	Х		Х	
Karnofsky Performance Status	Х	Х	Х		Х	
MRI scan / Tumor Assessments	X ⁴			X ⁸	X ^{8,13}	
ECG	Х	X ¹⁵	X ¹⁵		X ¹³	
ECHO (with ejection fraction)	Х		X ¹¹		X ¹¹	
CBC w/differential & platelets ⁵	Х	X ¹⁴	Х		Х	
Serum Chemistries ^{5,6}	Х	X ¹⁴	Х		Х	
Urinalysis ⁷	Х				Х	
Serum/Urine Pregnancy Test	Х					
ALDOXORUBICIN Administration		Х	Х			
Concomitant Medications ⁹	Х	Х	Х		Х	
Adverse Events ¹⁰		Х	Х		Х	
Telephone Follow-Up						Х

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: <u>1-310-674-6711</u>

SAFETY FAX: <u>1-310-826-6139</u>

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

CONFIDENTIAL

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SYNOPSIS

Name of S	ponsor/Compan	v: CvtRx (Corporation

Protocol Number:	Phase of Development: 2
ALDOXORUBICIN-P2-GBM-01	

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/m² (260 mg/m² doxorubicin equivalent) or 250 mg/m² (185 mg/m² 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/m² 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.

Dre	otocol Number:	Phase of Development: 2					
	DOXORUBICIN-P2-GBM-01	hase of Development: 2					
Stu	udy Population and Main Criteria	for Inclusion/Exclusion:					
	clusion Criteria:						
Sul	bjects must meet the following crite	ria 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.							
 Radiographic progression by RANO Working Group Criteria (see Appendix F) will be confirmed by Imaging Endpoints, a central imaging vendor; or 							
1		by if conducted within 4 weeks of Randomization.					
4.	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 cortico	steroids for at least 7 days prior to Randomization.					
6.	Capable of providing informed conse	ent and complying with trial procedures.					
7.							
8.	. Life expectancy ≥8 weeks.						
9. Measurable tumor lesions according to RANO Working Group Criteria (see Appendix F).							
	to screening, the subject m	on-measureable" disease due to a radical surgical resection prior nay still qualify if Inclusion #3(b) is met.					
10.	sterile, or practicing adequate birth of	e pregnant (e.g. post-menopausal for at least 1 year, surgically control methods) for the duration of the study. (Adequate eption, implanted contraception, intrauterine device implanted for 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, appointment and evaluation.	i.e. the ability to come to the study site for each scheduled					
	clusion Criteria:						
Sub	bjects meeting the following criteria w	ill not be enrolled:					
1.	Prior exposure to an anthracycline.						
2.	radiation and temozolomide.	ent of recurrent tumor after first line treatment with surgery,					
3.							
4. -							
5.	Exposure to any investigational age	-					
6.	carcinoma <i>in situ</i> of the cervix) unles	ot cured basal cell carcinoma, superficial bladder cancer or ss documented free of cancer for ≥3 years.					
7.	aminotransferase (ALT) > 2.5×ULN, <1,500/mm ³ , platelet concentration	n creatinine >1.5× upper limit of normal (ULN), alanine total bilirubin >1.5×ULN, absolute neutrophil count (ANC) <100,000/mm ³ , absolute lymphocyte count <1000/mm ³ , or <30% for males, serum albumin ≤2.5 g/dL, prothrombin time					
		(INR) >1.5×ULN or >3×ULN on anticoagulant with no evidence of					

Name of Sponsor/Company: CytR						
Protocol Number: ALDOXORUBICIN-P2-GBM-01	Phase of Development: 2					
8. Anion gap > 16 meq/L or arteria	al blood pH < 7.30.					
 Evidence of central nervous system (CNS) hemorrhage Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 on baseline magnetic resonance imaging (MRI). 						
 Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (see Appendix D). 						
 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). 						
	r previous history of QT prolongation.					
	ary 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.						
 Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals, or anti-fungals. 						
16. History of HIV infection.						
17. Major surgery, except diagnosti	c 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 a	nd could jeopardize the subject's participation in the study.					
Number of Subjects: Up to 28 subjects will be enrolled (1	4 at each dose level) in 3-5 study centers in the US.					
sterile solution of 50:50 ethanol:water reconstituted) as a 30 minute IV infu	Administration: tain 200 mg of ALDOXORUBICIN reconstituted by adding a er, administration completed within 2 hours (of being usion in Lactated Ringer's solution. Total doses of either equivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents).					
Reference Therapy, Dose and Mo None	de of Administration:					
Criteria for Evaluation:						
Efficacy: The following efficacy variables will • PFS • OS	be evaluated as noted:					
	Working Group Criteria [see Appendix F]) onths					
	SC-MRI in subjects who undergo additional MRI sequence					
 Pseudo progression events on DS evaluation 	, ,					

ALDOXORUBICIN-P2-GBM-01

Name of Sponsor/Company: CytRx Corporation

Protocol Number:

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.

	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	Х					
Review Inclusion/Exclusion		Х				
Medical History ¹	Х					
Physical Examination	Х	Х	Х		Х	
Height (cm)	Х					
Weight (kg)	Х	Х	Х			
BSA Calculation ²		Х	Х			
Vital Signs ³	Х	Х	Х		Х	
Karnofsky Performance Status	Х	Х	Х		Х	
MRI scan / Tumor Assessments	X4			X ⁸	X ^{8,13}	
ECG	Х	X ¹⁵	X ¹⁵		X ¹³	
ECHO (with ejection fraction)	Х		X ¹¹		X ¹¹	
CBC w/differential & platelets ⁵	Х	X ¹⁴	Х		Х	
Serum Chemistries ^{5,6}	X*	X ¹⁴	Х		Х	
Urinalysis ⁷	Х				Х	
Serum/Urine Pregnancy Test	Х					
ALDOXORUBICIN Administration		Х	Х			
Concomitant Medications ⁹	Х	Х	Х		Х	
Adverse Events ¹⁰		Х	Х		Х	
Telephone Follow-Up						Х

APPENDIX A:	Schedule of Treatment and Evaluations
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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:

11726 San Vicente Blvd Los Angeles, CA 90049 (310) 826-5648 FAX: (310) 826-6139

CytRx Corporation

SAFETY HOTLINE: <u>1-310-674-6711</u>

SAFETY FAX: <u>1-310-826-6139</u>

DATE OF PROTOCOL: August 9, 2013

CONFIDENTIAL

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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 Stud	ly 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:

Phase of Development: 2

Study Design and Methodology:

ALDOXORUBICIN-P2-GBM-01

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at either 350 mg/m² (260 mg/m² doxorubicin equivalent) or 250 mg/m² (185 mg/m² 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: Phase of Development: 2 ALDOXORUBICIN-P2-GBM-01 Phase of Development: 2						
Stu	udy Population and Main Criter	ia for Inclusion/Exclusion:				
Inc	clusion Criteria:					
Subjects must meet the following criteria to be included in the study:						
1.	Age ≥18 years of age; male or f	emale.				
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.
- 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/mm³, platelet concentration <100,000/mm³, absolute lymphocyte count <1000/mm³, 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).
- 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.

Protocol Number: ALDOXORUBICIN-P2-GBM-01	Phase of Development: 2
 Active, clinically significant seri anti-fungals. History of HIV infection. 	ous infection requiring treatment with antibiotics, anti-virals, or
of the study results.	ere with the subject's participation in the study or in the evaluation
-	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.
sterile solution of 50/50 ethanol:wa reconstituted) as a 30 minute IV inf	Administration: ntain 200 mg of ALDOXORUBICIN reconstituted by adding a ter, administration completed within 2 hours (of being fusion in Lactated Ringer's solution. Total doses of either 350 nivalent) or 250 mg/m ² (185 mg/m ² doxorubicin equivalents).
Reference Therapy, Dose and Me None	ode of Administration:
Criteria for Evaluation:	
Efficacy: The following efficacy variables wil • PFS • OS	l be evaluated as noted:
	D Working Group Criteria [see Appendix F]) see Appendix B)
Corticosteroid usage	
 Corticosteroid usage Safety: The following safety variables will b AEs 	be assessed over the course of the study:

ALDOXORUBICIN-P2-GBM-01

Name of Sponsor/Company: CytRx Corporation
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Protocol Number:

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 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.

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

APPENDIX A: Schedule of Treatment and Evaluations

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