CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-KS-01**
STUDY DRUG:	**ALDOXORUBICIN**
IND NUMBER:	**113,695**
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:	**December 02, 2013**

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma	
Primary Objectives: 1. Determine the preliminary efficacy of administration of ALDOXORUBICIN for HIV-infected patients with Kaposi's Sarcoma (KS). 2. 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. **Secondary Objectives:** 1. Evaluate the intratumoral kinetics of ALDOXORUBICIN and related biomarker expression through sequential biopsies of KS skin lesions. 2. Determine the change in performance status (PS) as measured by the Karnofsky Performance Status (KPS) (Appendix B).	
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 pro-drug has demonstrated enhanced antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. KS remains the most common HIV-associated tumor worldwide. Liposomal doxorubicin represents the standard of care for severe dermatologic/systemic KS, but a significant portion, if not the majority, of patients exhibit minimal to no clinical response to this agent, especially those with visceral disease, poor immune status at the time of therapy, and a history of HIV-associated opportunistic infections (OIs). The acidic tumor microenvironment of KS lesions is suitable for cleavage of the acid labile linker of ALDOXORUBICIN. Furthermore, minimal to no hematologic toxicities have been demonstrated for ALDOXORUBICIN in Phase 1 trials at doses equivalent to and exceeding the dose for liposomal doxorubicin recommended for KS treatment (27 mg/m^2 for ALDOXORUBICIN, equivalent to 20 mg/m^2 liposomal doxorubicin). Given the large number of skin lesions typically exhibited by HIV+ patients with KS, with or without systemic disease, longitudinal analyses of intratumoral drug concentrations and biomarker expression are also feasible.	

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

Study Design and Methodology:

This is an open-label phase 2 pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at 50, 100 or 150 mg/m^2 (37, 75, and 110 mg/m^2 doxorubicin equivalents) by intravenous infusion (IVI) to 10 patients in each group. Patients will receive ALDOXORUBICIN on Day 1, then every 3 weeks until evidence of tumor progression, unacceptable toxicity or withdrawal of consent.

Staging will be assessed at screening, then every even cycle using the AIDS Clinical Trials Group (ACTG) tumor, immune system, systemic illness (TIS) criteria (Appendix G), and treatment will continue every 3 weeks until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Response to therapy will be determined through evaluation of skin lesions (number, size, and nodularity). Chest computed tomography (CT) and abdominal magnetic resonance imaging (MRI) will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions. Subjects will visit the LSU Clinical and Translational Research Center every 3 weeks for their IVIs, at which time safety monitoring (including AEs) a directed physical examination, laboratory evaluations (serum chemistries, complete blood count [CBC], and urinalysis), vital signs, weight, KPS (Appendix B), ECHO evaluations, and ECGs will be performed.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-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. HIV (confirmed by ELISA and western blot) with histologically confirmed KS.
3. Willing to undergo serial tumor biopsies.
4. Capable of providing informed consent and complying with trial procedures.
5. KPS ≥70 (Appendix B)
6. Easter Cooperative Oncology Group (ECOG) PS 0-2.
7. Life expectancy ≥8 weeks.
8. Measurable (at accessible site or radiographic) tumor lesions according to ACTG TIS criteria (Appendix G).
9. 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.)
10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to an anthracycline.
2. Surgery and/or radiation treatment < 4 weeks prior to Randomization.
3. Exposure to any investigational agent within 30 days of Randomization.
4. 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.
5. 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 <75,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <25% for females or <27% for males, serum albumin ≤2.5 g/dL.
6. Evidence of central nervous system (CNS) hemorrhage National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 (published 28 May 2009) (Appendix C) grade 2 or greater on baseline MRI.
7. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines.
8. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
9. History or signs of active coronary artery disease with or without angina pectoris.
10. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.
11. Active, clinically significant serious infection requiring treatment with antibacterial, antiviral (other than antiretroviral therapy), or antifungal therapy.
12. Major surgery within 4 weeks prior to Randomization.
13. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
14. Any condition that is unstable and could jeopardize the subject's participation in the study.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Number of Subjects: Up to 30 subjects will be enrolled (10 in each arm) at the Louisiana State University (LSU) Health Science Center in New Orleans, LA.	
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% ethanol: 50% water, administration completed within 2 hours (of being reconstituted) as a 30 minute IVI in Lactated Ringer's solution. Total doses of either 50, 100, or 150 mg/m^2 will be administered at infusion visits.	
Reference Therapy, Dose and Mode of Administration: None	

Criteria for Evaluation:

Efficacy:

- The following efficacy variables will be evaluated every even cycle:
    1. Tumor staging (ACTG TIS criteria [Appendix G])
    2. Number of skin lesions (if applicable)
    3. Size of individual skin lesions (if applicable)
    4. Nodularity of skin lesions (if applicable)
- Chest CT and abdominal MRI will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions.

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

Tumor Pathology:

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

- Concentration of drug within skin tumors and adjacent normal skin will be assessed using HPLC in the laboratory of Dr. Om Prakash in the Louisiana Cancer Research Center.
- Routine histopathologic assessments and expression of KSHV-encoded LANA, secreted protein acidic and rich in cysteine (SPARC), gp60, and caveolin (which may relate to mechanisms of drug activity) within skin tumors will be assessed by Dr. Luis Del Valle in the Molecular and Histology Core Facility in the Louisiana Cancer Research Center. Expression will be assessed quantitatively using immunofluorescence analyses and fluorescence intensity quantification software. (Appendix F).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-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.

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, ECHO evaluations, ECG results, 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	Cycle 4	Every Odd Cycle	Every Even 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		X[2]	X[2]					
Vital signs[3]	X	X	X				X	
KPS	X	X	X				X	
Tumor measurements[4]	X[16]			X[8]			X[8]	
ECG	X	X			X		X[15]	
ECHO (with ejection fraction)	X			X[11]			X	
CBC w/differential & plts[5]	X	X	X				X	
Serum chemistries[5,6]	X	X	X				X	
Urinalysis[7]	X						X	
Serum/urine pregnancy test	X							
ALDOXORUBICIN administration[14]		X	X					
Concomitant medications[9]	X	X	X				X	
Biopsy of tumor						X[13]		
AEs[10]	X	X	X				X	
Telephone follow-up[12]								X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (Section 5 for details).

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-KS-01**
STUDY DRUG:	**ALDOXORUBICIN**
IND NUMBER:	**113,695**
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:	**December 02, 2013**
AMENDMENT 1:	**February 05, 2014**

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma	
Primary Objectives: 1. Determine the preliminary efficacy of administration of ALDOXORUBICIN for HIV-infected patients with Kaposi's Sarcoma (KS). 2. 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. **Secondary Objectives:** 1. Evaluate the intratumoral kinetics of ALDOXORUBICIN and related biomarker expression through sequential biopsies of KS skin lesions. 2. Determine the change in performance status (PS) as measured by the Karnofsky Performance Status (KPS) (Appendix B).	
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 pro-drug has demonstrated enhanced antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. KS remains the most common HIV-associated tumor worldwide. Liposomal doxorubicin represents the standard of care for severe dermatologic/systemic KS, but a significant portion, if not the majority, of patients exhibit minimal to no clinical response to this agent, especially those with visceral disease, poor immune status at the time of therapy, and a history of HIV-associated opportunistic infections (OIs). The acidic tumor microenvironment of KS lesions is suitable for cleavage of the acid labile linker of ALDOXORUBICIN. Furthermore, minimal to no hematologic toxicities have been demonstrated for ALDOXORUBICIN in Phase 1 trials at doses equivalent to and exceeding the dose for liposomal doxorubicin recommended for KS treatment (27 mg/m^2 for ALDOXORUBICIN, equivalent to 20 mg/m^2 liposomal doxorubicin). Given the large number of skin lesions typically exhibited by HIV+ patients with KS, with or without systemic disease, longitudinal analyses of intratumoral drug concentrations and biomarker expression are also feasible.	

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

Study Design and Methodology:

This is an open-label phase 2 pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at 50, 100 or 150 mg/m^2 (37, 75, and 110 mg/m^2 doxorubicin equivalents) by intravenous infusion (IVI) to 10 patients in each group. Patients will receive ALDOXORUBICIN on Day 1, then every 3 weeks until evidence of tumor progression, unacceptable toxicity or withdrawal of consent.

Staging will be assessed at screening, then every even cycle using the AIDS Clinical Trials Group (ACTG) tumor, immune system, systemic illness (TIS) criteria (Appendix G), and treatment will continue every 3 weeks until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Response to therapy will be determined through evaluation of skin lesions (number, size, and nodularity). Chest computed tomography (CT) and abdominal magnetic resonance imaging (MRI) will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions. Subjects will visit the LSU Clinical and Translational Research Center every 3 weeks for their IVIs, at which time safety monitoring (including AEs) a directed physical examination, laboratory evaluations (serum chemistries, complete blood count [CBC], and urinalysis), vital signs, weight, KPS (Appendix B), ECHO evaluations, and ECGs will be performed.

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

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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1. Age ≥18 years of age; male or female.
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10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure > 120 mg/m^2 of pegylated liposomal doxorubicin (Doxil).
2. Surgery and/or radiation treatment < 4 weeks prior to Randomization.
3. Exposure to any investigational agent within 30 days of Randomization.
4. 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.
5. 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 <75,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <25% for females or <27% for males, serum albumin ≤2.5 g/dL.
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Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Number of Subjects: Up to 30 subjects will be enrolled (10 in each arm) at the Louisiana State University (LSU) Health Science Center in New Orleans, LA.	
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% ethanol: 50% water, administration completed within 2 hours (of being reconstituted) as a 15-minute IVI at the 50 mg/m^2 dose or 30-minute IVI at the 100 or 150 mg/m^2 dose in Lactated Ringer's solution. Total doses of either 50, 100, or 150 mg/m^2 will be administered at infusion visits.	
Reference Therapy, Dose and Mode of Administration: None	

Criteria for Evaluation:

Efficacy:

- The following efficacy variables will be evaluated every even cycle:
    1. Tumor staging (ACTG TIS criteria [Appendix G])
    2. Number of skin lesions (if applicable)
    3. Size of individual skin lesions (if applicable)
    4. Nodularity of skin lesions (if applicable)
- Chest CT and abdominal MRI will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions.

Safety:

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

- AEs
- Ability to remain on assigned treatment (tolerability)
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Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-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.

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, ECHO evaluations, ECG results, 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	Cycle 4	Every Odd Cycle	Every Even 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		X[2]	X[2]					
Vital signs[3]	X	X	X				X	
KPS	X	X	X				X	
Tumor measurements[4]	X[16]			X[8]			X[8]	
ECG	X	X			X		X[15]	
ECHO (with ejection fraction)	X			X[11]			X	
CBC w/differential & plts[5]	X	X	X				X	
Serum chemistries[5,6]	X	X	X				X	
Urinalysis[7]	X						X	
Serum/urine pregnancy test	X							
ALDOXORUBICIN administration[14]		X	X					
Concomitant medications[9]	X	X	X				X	
Biopsy of tumor						X[13]		
AEs[10]	X	X	X				X	
Telephone follow-up[12]								X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (Section 5 for details).

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-KS-01**
STUDY DRUG:	**ALDOXORUBICIN**
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SAFETY HOTLINE:	**1-310-674-6711**
SAFETY FAX:	**1-310-826-6139**
ORIGINAL PROTOCOL:	**December 02, 2013**
AMENDMENT 1:	**February 05, 2014**
AMENDMENT 2:	**April 07, 2014**

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma	
Primary Objectives: 1. Determine the preliminary efficacy of administration of ALDOXORUBICIN for HIV-infected patients with Kaposi's Sarcoma (KS). 2. 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. **Secondary Objectives:** 1. Evaluate the intratumoral kinetics of ALDOXORUBICIN and related biomarker expression through sequential biopsies of KS skin lesions. 2. Determine the change in performance status (PS) as measured by the Karnofsky Performance Status (KPS) (Appendix B).	
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Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2

Study Design and Methodology:

This is an open-label phase 2 pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at 50, 100 or 150 mg/m^2 (37, 75, and 110 mg/m^2 doxorubicin equivalents) by intravenous infusion (IVI) to 10 patients in each group. Patients will receive ALDOXORUBICIN on Day 1, then every 3 weeks until evidence of tumor progression, unacceptable toxicity or withdrawal of consent.

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Protocol Number: ALDOXORUBICIN-P2-KS-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.
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3. Willing to undergo serial tumor biopsies.
4. Capable of providing informed consent and complying with trial procedures.
5. KPS ≥70 (Appendix B)
6. Easter Cooperative Oncology Group (ECOG) PS 0-2.
7. Life expectancy ≥8 weeks.
8. Measurable (at accessible site or radiographic) tumor lesions according to ACTG TIS criteria (Appendix G).
9. 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.)
10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure > 375 mg/m^2 of doxorubicin or pegylated liposomal doxorubicin (Doxil).
2. Surgery and/or radiation treatment < 4 weeks prior to Randomization.
3. Exposure to any investigational agent within 30 days of Randomization.
4. 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.
5. 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 <75,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <25% for females or <27% for males, serum albumin ≤2.5 g/dL.
6. Evidence of central nervous system (CNS) hemorrhage National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 (published 28 May 2009) (Appendix C) grade 2 or greater on baseline MRI.
7. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines.
8. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
9. History or signs of active coronary artery disease with or without angina pectoris.
10. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.
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13. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
14. Any condition that is unstable and could jeopardize the subject's participation in the study.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Number of Subjects: Up to 30 subjects will be enrolled (10 in each arm) at the Louisiana State University (LSU) Health Science Center in New Orleans, LA.	
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% ethanol: 50% water, administration completed within 2 hours (of being reconstituted) as a 15-minute IVI at the 50 mg/m^2 dose or 30-minute IVI at the 100 or 150 mg/m^2 dose in Lactated Ringer's solution. Total doses of either 50, 100, or 150 mg/m^2 will be administered at infusion visits.	
Reference Therapy, Dose and Mode of Administration: None	

Criteria for Evaluation:

Efficacy:

- The following efficacy variables will be evaluated every even cycle:
    1. Tumor staging (ACTG TIS criteria [Appendix G])
    2. Number of skin lesions (if applicable)
    3. Size of individual skin lesions (if applicable)
    4. Nodularity of skin lesions (if applicable)
- Chest CT and abdominal MRI will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions.

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

Tumor Pathology:

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

- Concentration of drug within skin tumors and adjacent normal skin will be assessed using HPLC in the laboratory of Dr. Om Prakash in the Louisiana Cancer Research Center.
- Routine histopathologic assessments and expression of KSHV-encoded LANA, secreted protein acidic and rich in cysteine (SPARC), gp60, and caveolin (which may relate to mechanisms of drug activity) within skin tumors will be assessed by Dr. Luis Del Valle in the Molecular and Histology Core Facility in the Louisiana Cancer Research Center. Expression will be assessed quantitatively using immunofluorescence analyses and fluorescence intensity quantification software. (Appendix F).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-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.

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, ECHO evaluations, ECG results, 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	Cycle 4	Every Odd Cycle	Every Even 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		X[2]	X[2]					
Vital signs[3]	X	X	X				X	
KPS	X	X	X				X	
Tumor measurements[4]	X[16]			X[8]			X[8]	
ECG	X	X			X		X[15]	
ECHO (with ejection fraction)	X			X[11]			X	
CBC w/differential & plts[5]	X	X	X				X	
Serum chemistries[5,6]	X	X	X				X	
Urinalysis[7]	X						X	
Serum/urine pregnancy test	X							
ALDOXORUBICIN administration[14]		X	X					
Concomitant medications[9]	X	X	X				X	
Biopsy of tumor						X[13]		
AEs[10]	X	X	X				X	
Telephone follow-up[12]								X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (Section 5 for details).

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-KS-01**
STUDY DRUG:	**ALDOXORUBICIN**
IND NUMBER:	**113,695**
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:	**December 02, 2013**
AMENDMENT 1:	**February 05, 2014**
AMENDMENT 2:	**April 07, 2014**
AMENDMENT 3:	**September 10, 2014**

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma	

Primary Objectives:

1. Determine the preliminary efficacy of administration of ALDOXORUBICIN for HIV-infected patients with Kaposi's Sarcoma (KS).
2. 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.

Secondary Objectives:

1. Evaluate the intratumoral kinetics of ALDOXORUBICIN and related biomarker expression through sequential biopsies of KS skin lesions only on samples obtained at LSU Medical Center.
2. Determine the change in performance status (PS) as measured by the Karnofsky Performance Status (KPS) (Appendix B).
3. Determine the change in quality of life as measured by the KS Functional Assessment of HIV (FAHI) Quality of Life instrument (QoLI) (Appendix H).

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 pro-drug has demonstrated enhanced antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin.

KS remains the most common HIV-associated tumor worldwide. Liposomal doxorubicin represents the standard of care for severe dermatologic/systemic KS, but a significant portion, if not the majority, of patients exhibit minimal to no clinical response to this agent, especially those with visceral disease, poor immune status at the time of therapy, and a history of HIV-associated opportunistic infections (OIs). The acidic tumor microenvironment of KS lesions is suitable for cleavage of the acid labile linker of ALDOXORUBICIN. Furthermore, minimal to no hematologic toxicities have been demonstrated for ALDOXORUBICIN in Phase 1 trials at doses equivalent to and exceeding the dose for liposomal doxorubicin recommended for KS treatment (27 mg/m^2 for ALDOXORUBICIN, equivalent to 20 mg/m^2 liposomal doxorubicin). Given the large number of skin lesions typically exhibited by HIV+ patients with KS, with or without systemic disease, longitudinal analyses of intratumoral drug concentrations and biomarker expression are also feasible.

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

Study Design and Methodology:

This is an open-label phase 2 pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at 100 or 150 mg/m^2 (75 and 110 mg/m^2 doxorubicin equivalents) by intravenous infusion (IVI) to 10 patients in each group. Patients will receive ALDOXORUBICIN on Day 1, then every 3 weeks until evidence of tumor progression, unacceptable toxicity or withdrawal of consent.

Staging will be assessed at screening, then every even cycle using the AIDS Clinical Trials Group (ACTG) tumor, immune system, systemic illness (TIS) criteria (Appendix G), and treatment will continue every 3 weeks until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Response to therapy will be determined through evaluation of skin lesions (number, size, and nodularity). Chest computed tomography (CT) and abdominal magnetic resonance imaging (MRI) will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions. Subjects will visit the clinical site every 3 weeks for their IVIs, at which time safety monitoring (including AEs) a directed physical examination, laboratory evaluations (serum chemistries, complete blood count [CBC], and urinalysis), vital signs, weight, KPS (Appendix B), ECHO evaluations, and ECGs will be performed. The FAHI QoLI will be administered at and at every fourth cycle.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-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. HIV (confirmed by ELISA and western blot) with histologically confirmed KS.
3. Willing to undergo serial tumor biopsies.
4. Capable of providing informed consent and complying with trial procedures.
5. KPS ≥70 (Appendix B)
6. Easter Cooperative Oncology Group (ECOG) PS 0-2.
7. Life expectancy ≥8 weeks.
8. Measurable (at accessible site or radiographic) tumor lesions according to ACTG TIS criteria (Appendix G).
9. 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.)
10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure > 375 mg/m^2 of doxorubicin or pegylated liposomal doxorubicin (Doxil).
2. Surgery and/or radiation treatment < 4 weeks prior to Randomization.
3. Exposure to any investigational agent within 30 days of Randomization.
4. 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.
5. 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 <75,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <25% for females or <27% for males, serum albumin ≤2.5 g/dL.
6. Evidence of central nervous system (CNS) hemorrhage National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (Appendix C) grade 2 or greater on baseline MRI.
7. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines.
8. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
9. History or signs of active coronary artery disease with or without angina pectoris.
10. Serious myocardial dysfunction defined as ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted institutional normal value.
11. Active, clinically significant serious infection requiring treatment with antibacterial, antiviral (other than antiretroviral therapy), or antifungal therapy.
12. Major surgery within 4 weeks prior to Randomization.
13. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
14. Any condition that is unstable and could jeopardize the subject's participation in the study.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Number of Subjects: Up to 20 subjects will be enrolled (10 in each arm) at 2-4 sites in the United States.	
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% ethanol: 50% water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI in Lactated Ringer's solution. Total doses of 100 or 150 mg/m^2 will be administered at infusion visits.	
Reference Therapy, Dose and Mode of Administration: None	

Criteria for Evaluation:

Efficacy:

- The following efficacy variables will be evaluated every even cycle:
    1. Tumor staging (ACTG TIS criteria [Appendix G])
    2. Number of skin lesions (if applicable)
    3. Size of individual skin lesions (if applicable)
    4. Nodularity of skin lesions (if applicable)
- Chest CT and abdominal MRI will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions.
- FAHI QoL Instrument at and every fourth cycle.

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

Tumor Pathology:

The following pathologic variables will be assessed over the course of the study only in subjects enrolled at the Louisiana State University (LSU) Health Science Center:

- Concentration of drug within skin tumors and adjacent normal skin will be assessed using HPLC in the laboratory of Dr. Om Prakash in the Louisiana Cancer Research Center.
- Routine histopathologic assessments and expression of KSHV-encoded LANA, secreted protein acidic and rich in cysteine (SPARC), gp60, and caveolin (which may relate to mechanisms of drug activity) within skin tumors will be assessed by Dr. Luis Del Valle in the Molecular and Histology Core Facility in the Louisiana Cancer Research Center. Expression will be assessed quantitatively using immunofluorescence analyses and fluorescence intensity quantification software. (Appendix F).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-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.

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, ECHO evaluations, ECG results, 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	Cycle 2	Cycle 4	Every Odd Cycle	Every Fourth 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		X[2]	X[2]						
Vital signs[3]	X	X	X					X	
KPS	X	X	X					X	
FAHI QoL	X						X		
Tumor measurements[4]	X[16]				X[8]			X[8]	
ECG	X	X				X		X[15]	
ECHO (with ejection fraction)	X				X[11]			X	
CBC w/differential & plts[5]	X	X	X					X	
Serum chemistries[5,6]	X	X	X					X	
Urinalysis[7]	X							X	
Serum/urine pregnancy test	X								
ALDOXORUBICIN administration[14]		X	X						
Concomitant medications[9]	X	X	X					X	
Biopsy of tumor[13]	X			X			X[13]		
AEs[10]	X	X	X					X	
Telephone follow-up[12]									X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (Section 5 for details).

CLINICAL PROTOCOL

TITLE:	**An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-KS-01**
STUDY DRUG:	**ALDOXORUBICIN**
IND NUMBER:	**113,695**
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:	**December 02, 2013**
AMENDMENT 1:	**February 05, 2014**
AMENDMENT 2:	**April 07, 2014**
AMENDMENT 3:	**September 10, 2014**
AMENDMENT 4:	**January 13, 2015**

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Title of the Protocol: An Open-Label Pilot Phase 2 Study to Investigate Efficacy, Safety, and Intratumoral Kinetics of ALDOXORUBICIN in HIV-Infected Patients with Kaposi's Sarcoma	

Primary Objectives:

1. Determine the preliminary efficacy of administration of ALDOXORUBICIN for HIV-infected patients with Kaposi's Sarcoma (KS).
2. 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.

Secondary Objectives:

1. Evaluate the intratumoral kinetics of ALDOXORUBICIN and related biomarker expression through sequential biopsies of KS skin lesions only on samples obtained at LSU Medical Center.
2. Determine the change in performance status (PS) as measured by the Karnofsky Performance Status (KPS) (Appendix B).
3. Determine the change in quality of life as measured by the KS Functional Assessment of HIV (FAHI) Quality of Life instrument (QoLI) (Appendix H).

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 pro-drug has demonstrated enhanced antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin.

KS remains the most common HIV-associated tumor worldwide. Liposomal doxorubicin represents the standard of care for severe dermatologic/systemic KS, but a significant portion, if not the majority, of patients exhibit minimal to no clinical response to this agent, especially those with visceral disease, poor immune status at the time of therapy, and a history of HIV-associated opportunistic infections (OIs). The acidic tumor microenvironment of KS lesions is suitable for cleavage of the acid labile linker of ALDOXORUBICIN. Furthermore, minimal to no hematologic toxicities have been demonstrated for ALDOXORUBICIN in Phase 1 trials at doses equivalent to and exceeding the dose for liposomal doxorubicin recommended for KS treatment (27 mg/m^2 for ALDOXORUBICIN, equivalent to 20 mg/m^2 liposomal doxorubicin). Given the large number of skin lesions typically exhibited by HIV+ patients with KS, with or without systemic disease, longitudinal analyses of intratumoral drug concentrations and biomarker expression are also feasible.

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

Study Design and Methodology:

This is an open-label phase 2 pilot study evaluating the preliminary efficacy and safety of ALDOXORUBICIN administered at 100 or 150 mg/m^2 (75 and 110 mg/m^2 doxorubicin equivalents) by intravenous infusion (IVI) to 10 patients in each group. Patients will receive ALDOXORUBICIN on Day 1, then every 3 weeks until evidence of tumor progression, unacceptable toxicity or withdrawal of consent.

Staging will be assessed at screening, then every even cycle using the AIDS Clinical Trials Group (ACTG) tumor, immune system, systemic illness (TIS) criteria (Appendix G), and treatment will continue every 3 weeks until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Response to therapy will be determined through evaluation of skin lesions (number, size, and nodularity). Chest computed tomography (CT) and abdominal magnetic resonance imaging (MRI) will be performed at baseline, prior to Cycle 4 and at end of treatment to evaluate visceral lesions. Subjects will visit the clinical site every 3 weeks for their IVIs, at which time safety monitoring (including AEs) a directed physical examination, laboratory evaluations (serum chemistries and complete blood count [CBC]), vital signs, weight, KPS (Appendix B), ECHO evaluations, and ECGs will be performed. All subjects will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. The FAHI QoLI will be administered at and at every fourth cycle.

Name of Sponsor/Company: CytRx Corporation

Protocol Number: ALDOXORUBICIN-P2-KS-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. HIV (confirmed by ELISA, western blot, OraQuick®, or viral loads) with histologically confirmed KS.
3. Willing to undergo serial tumor biopsies.
4. Capable of providing informed consent and complying with trial procedures.
5. KPS ≥70 (Appendix B)
6. Easter Cooperative Oncology Group (ECOG) PS 0-2.
7. Life expectancy ≥8 weeks.
8. Measurable (at accessible site or radiographic) tumor lesions according to ACTG TIS criteria (Appendix G).
9. 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.)
10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure > 375 mg/m^2 of doxorubicin or pegylated liposomal doxorubicin (Doxil).
2. Surgery and/or radiation treatment < 4 weeks prior to Randomization.
3. Exposure to any investigational agent within 30 days of Randomization.
4. 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.
5. 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 <75,000/mm^3, absolute lymphocyte count <1000/mm^3, hematocrit level <25% for females or <27% for males, serum albumin ≤2.5 g/dL.
6. Anion gap > 16 meq/L or arterial blood pH <7.30.
7. Evidence of central nervous system (CNS) hemorrhage National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (Appendix C) grade 2 or greater on baseline MRI.
8. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines.
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.
12. Active, clinically significant serious infection requiring treatment with antibacterial, antiviral (other than antiretroviral therapy), or antifungal therapy.
13. Major surgery within 4 weeks prior to Randomization.
14. Any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
15. Any condition that is unstable and could jeopardize the subject's participation in the study.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-01	**Phase of Development:** 2
Number of Subjects: Up to 20 subjects will be enrolled (10 in each arm) at 2-4 sites in the United States.	
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% ethanol: 50% water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI in Lactated Ringer's solution. Total doses of 100 or 150 mg/m^2 will be administered at infusion visits.	
Reference Therapy, Dose and Mode of Administration: None	

Criteria for Evaluation:

Efficacy:

- The following efficacy variables will be evaluated every even cycle:
    1. Tumor staging (ACTG TIS criteria [Appendix G])
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- FAHI QoL Instrument at and every fourth cycle.

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
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Tumor Pathology:

The following pathologic variables will be assessed over the course of the study only in subjects enrolled at the Louisiana State University (LSU) Health Science Center:

- Concentration of drug within skin tumors and adjacent normal skin will be assessed using HPLC in the laboratory of Dr. Om Prakash in the Louisiana Cancer Research Center.
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Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-KS-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.

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, ECHO evaluations, ECG results, 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.

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Review inclusion/exclusion		X							
Medical history[1]	X								
Physical examination	X	X	X					X	
Height (cm)	X								
Weight (kg)	X	X	X						
BSA calculation		X[2]	X[2]						
Vital signs[3]	X	X	X					X	
KPS	X	X	X					X	
FAHI QoL	X						X		
Tumor measurements[4]	X[16]				X[8]			X[8]	
ECG	X	X				X		X[15]	
ECHO (with ejection fraction)	X				X[11]			X	
CBC w/differential & plts[5]	X	X	X					X	
Serum chemistries[5,6]	X*	X	X					X	
Urinalysis[7]	X							X	
Serum/urine pregnancy test	X								
ALDOXORUBICIN administration[14]		X	X						
Concomitant medications[9]	X	X	X					X	
Biopsy of tumor[13]	X			X			X[13]		
AEs[10]	X	X	X					X	
Telephone follow-up[12]									X

NOTE: All assessments must be performed within 72 hours of each specified time parameter, except Cycle 1 (Section 5 for details).

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