CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy**

PROTOCOL NUMBER:	**ALDOXORUBICIN-P3-STS-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**113,695**
EUDRACT NUMBER:	**2013-004103-40**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**Toll-free: TBD**
SAFETY FAX:	**Toll-free: TBD**
DATE OF PROTOCOL:	**April 3, 2013**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation (CytRx) prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partner] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CytRx.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: 

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: March 3, 2014

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator's choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS). **Secondary Objectives:** The secondary objectives of this study are to evaluate the efficacy of aldoxorubicin as measured by OS, safety of aldoxorubicin compared to investigator's choice 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, as well as disease control rate, tumor response and quality of life (quality of life evaluation will only be used for exploratory purposes). **Exploratory Objectives:** To determine the pharmacokinetics (PK) of aldoxorubicin, doxorubicin, and doxorubicinol following intravenous (IV) administration of aldoxorubicin, and to evaluate the exposure-response relationships between aldoxorubicin, doxorubicin, and/or doxorubicinol and PFS, OS, and selected safety parameters.	
Study Rationale and Significance: Aldoxorubicin (INNO-206; DOXO-EMCH) 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 antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas who have failed prior chemotherapies have a poor prognosis with PFS of around 2-4.6 months and median OS of approximately 9-12 months. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as ifosfamide, gemcitabine, docetaxel, vinorelbine, dacarbazine, temozolomide, epirubicin, pazopanib and liposomal doxorubicin. However, these regimens can be quite toxic and have not significantly impacted either progression-free or OS in these individuals. Pazopanib, recently approved in the US and Europe, does appear to extend PFS in soft tissue sarcoma patients (except liposarcomas) who have relapsed after receiving prior chemotherapy compared to no treatment, but does not increase OS. Aldoxorubicin may improve upon the activity of doxorubicin without an increase in toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Design and Methodology:

This is a phase 3 open-label study evaluating the efficacy and safety of aldoxorubicin administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days for up to 8 cycles compared to investigator's choice of treatment among 5 different therapies. These therapies include: 1) dacarbazine administered at 1000 mg/m^2 by intravenous infusion (IVI), over 90±15 minutes on Day 1 every 21 days for up to 8 consecutive cycles; 2) pazopanib, 800 mg orally each day until tumor progression or unacceptable toxicity occurs; 3) gemcitabine, 900 mg/m^2 by IVI over 90 minutes on Days 1 and 8, plus docetaxel, 100 mg/m^2 by IVI over 1 hour on Day 8 of a 28 day cycle for up to 8 cycles; 4) doxorubicin, 75 mg/m^2 by IVI over 5 to 30 minutes every 21 days for up to 8 cycles or a maximum cumulative dose of 550 mg/m^2; or 5) ifosfamide 2.0 g/m^2 administered over 2 to 4 hours on Days 1-4 of a 21 day cycle + mesna per standard site administration regimen for up to 8 cycles. The investigative site must **pre-specify** their choice of treatments for the comparator arm to be used at their site, and no more than 3 treatment regimens may be selected for the comparator arm at each site which must be selected **prior** to the study site initiation visit. Subjects will be randomized 1:1 to receive either aldoxorubicin or investigator's choice of up to 3 control regimens pre-selected by the study site. Pretreatment with G-CSF is permitted according to ASCO Guidelines (Appendix E).

All Screening requirements, including an ECHO exam, must be completed within 28 days of the Cycle 1-Day 1 visit. Subjects receiving aldoxorubicin, ifosfamide, dacarbazine or doxorubicin will visit the study site on Day 1 of each cycle. They will have complete blood counts (CBC) and serum chemistries on Day 15 and Day 21 (if Day 21 does not correspond to Day 1 of the next cycle, ±3 days; Day 28 for subjects taking pazopanib) of each cycle as well. Subjects receiving pazopanib will visit the study site on Day 1 of their next cycle for monitoring, testing (same as for Day 1 for other treatment regimens) and to receive a new supply of study drug. Subjects receiving gemcitabine plus docetaxel will visit the study site on both days of their infusions (Days 1 and 8) and at Day 21 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, CBC, and urinalysis), vital signs, weight measurements, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and ECGs will be performed on Day 1 (for all subjects) of each cycle. Cardiac function will also be followed periodically (per Schedule of Treatment and Evaluations in Appendix A) with ECHOs for subjects receiving either aldoxorubicin or doxorubicin. Treatment will continue until tumor progression is observed, 8 cycles of treatment are completed (except for pazopanib), subject asks to withdraw, unacceptable toxicity occurs, a change in therapy would be in the best interest of the subject, subject becomes pregnant or fails to use adequate birth control, need for any treatment not allowed by the protocol, or subject is non-compliant with study requirements.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[50] OS, PFS, and PFS at 4 and 6 months will be evaluated. Objective overall response rate (ORR) (complete and partial responses [PRs]), disease control rate (objective responses plus stable disease at 4 months) and quality of life will be assessed.

The PK of aldoxorubicin, doxorubicin, and doxorubicinol will be evaluated using a sparse sample analysis. Plasma samples will be collected at Cycle 1 at the following time points: the end of the infusion, between 1.5 and 4 hours from the end of the infusion, and on Days 2, and 3. If necessary and possible, PK samples may be collected at a later cycle.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Has provided written informed consent prior to any study related activities.
2. Age ≥15 years (US only), and 18-80 (rest of world (ROW)), male or female.
3. Histological confirmation of intermediate or high grade soft-tissue sarcoma. Tissue must be sent to a central pathology lab for review but will not preclude entry onto the study. **Final assignment of tumor grade and histology will be based on the designation provided by the central pathology review.**
4. **An adequate tumor specimen obtained by either excisional biopsy, inclusion biopsy or core needle biopsy must be sent to the central pathology lab for evaluation. The material must measure at least 0.8 × 0.1 cm in size or contain at least 50 tumor cells.**
5. Locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade with evidence of disease progression by either computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinical judgment on or after the last cancer therapy within 6 months prior to randomization.
6. Relapsed or refractory (lack of response) to ≥1 course of systemic therapy regimen(s), excluding adjuvant or neoadjuvant chemotherapy, and is incurable by either surgery or radiation.
7. Capable of providing informed consent and complying with trial procedures.
8. ECOG PS 0-2.
9. Life expectancy >12 weeks.
10. Measurable tumor lesions according to RECIST 1.1 criteria.[50]
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. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 11 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and agree to continue use for 6 months after the final dose of study treatment.
13. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
14. Accessibility to the site that optimizes the subject's ability to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Palliative surgery and/or radiation treatment <4 weeks prior to date of randomization.
3. Exposure to any investigational agent within 30 days of date of randomization.
4. Exposure to any systemic chemotherapy within 28 days of date of randomization.
5. An inadequate tumor specimen as defined by the central pathologist.
6. Current evidence/diagnosis of alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma (unless transformed to fibrosarcoma), Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas.
7. Evidence of central nervous system (CNS) metastasis who have not received prior definitive therapy for their lesions.
8. History of other malignancies except cured basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma *in situ*, superficial bladder cancer or carcinoma *in situ* of the cervix unless documented free of cancer for ≥5 years.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

9. Laboratory values: Screening serum creatinine >1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, hemoglobin <9 g/dL.
10. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) (Appendix D) guidelines.
11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications.
13. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
14. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
15. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
16. Known history of HIV infection.
17. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals. The Medical Monitor should be contacted for any uncertainties.
18. Major surgery within 4 weeks prior to date of randomization.
19. Current or past substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
20. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:

Approximately 400 subjects with metastatic, locally advanced or unresectable soft tissue sarcomas who have either not responded to or have progressed after treatment with 1 or more systemic regimens of non-adjuvant chemotherapies will be randomized 1:1 (aldoxorubicin:investigator's choice) at approximately 75 study centers in the US, Europe, China, Canada, Latin America and Australia. The randomization will be stratified according to their initial PS (ECOG 0-1 vs 2), whether they had either 1 prior systemic non-adjuvant chemotherapy regimens or >1 prior systemic non-adjuvant chemotherapy regimens and whether they had received prior doxorubicin chemotherapy. Subjects will also be stratified by their histopathological diagnosis as determined by the local site. The four stratification groups will be leiomyosarcomas, liposarcoma, synovial sarcoma, and all other sarcomas.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Test Product, Dose and Mode of Administration:

Aldoxorubicin: Lyophilized powder in vials that contain 200 mg of aldoxorubicin reconstituted by adding a solution of 50% ethanol: 50% sterile water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Investigator's Choice: Up to three treatment regimens are to be chosen by the investigator from the list above prior to the initiation of the study site and the treatment chosen for each subject enrolled in the study must be entered into the case report form.

Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, Sterile Water for Injection, USP. The resulting solution contains 10 mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously. The reconstituted solution may be further diluted with 5% dextrose injection, or sodium chloride injection (250 to 500 mL), and administered as an IVI over 90±15 minutes.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Pazopanib (Votrient®) 200 mg tablets can be stored at room temperature between 20° and 25°C; excursions are permitted between 15° and 30°C. Tablets are taken 1 hour before or 2 hours after a meal and tablets are NOT to be crushed.

Gemcitabine 200 mg or 1 g lyophilized powder in a single use vial is reconstituted with 0.9% NaCl to a final concentration of ≤40 mg/mL and pH 2.7 to 3.3. The reconstituted solution may be further diluted with 0.9% NaCl and administered by IVI in <60 minutes. It is stable for up to 24 hours at controlled room temperature
(20° to 25°C) and should not be refrigerated.

Docetaxel 80 mg/2 mL and 20 mg/0.5 mL with diluents for both strengths (13% [w/w] ethanol in water for injection) is administered by IVI over approximately 60 minutes after dilution into a 250 to 500 mL infusion bag of either 0.9% NaCl or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. Docetaxel final dilution for infusion should be administered within 4 hours of preparation. It can be stored between 2° and 25°C.

Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose and may be administered over 5 to 30 minutes.

Ifosamide single-dose vials for constitution and administration by IVI each contain 1 gram or 3 grams of sterile ifosfamide, USP. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Sterile Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved) to the vial and shaking to dissolve. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose solution and may be administered over 2 to 4 hours.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Criteria for Evaluation:

Efficacy:

The following efficacy variables will be evaluated as noted:

- PFS.
- OS.
- Objective tumor response (RECIST 1.1 criteria[50]).
- Disease control rate (objective tumor response + stable disease at 4 months).
- Subject Reported Outcome as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire.

Safety:

The following safety variables will be assessed over the duration 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.

Pharmacokinetics:

The following PK variables will be assessed for aldoxorubicin, doxorubicin, and doxorubicinol:

- Maximum drug concentration (C_{max}) in plasma.
- Area under the plasma drug-concentration-time profile (AUC).
- Clearance (CL).
- Volume of distribution (V_d).
- Half-life ($t_{½}$).

Name of Sponsor/Company: CytRx Corporation	
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Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects will be evaluated for efficacy. All subjects who receive at least 1 dose of study medication will be evaluated for safety.

Efficacy:
The primary analysis of PFS will be carried out when approximately 191 PFS events have been observed (approximately 15 months following the completion of enrollment of 400 subjects). Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

An important secondary endpoint is overall survival (OS). The analysis of OS will be considered confirmatory only if the PFS analysis is statistically significant. As a result, the nominal level of significance for the OS analysis will be α=0.05. However, because an interim analysis of OS will be carried out at the time of the analysis of PFS, the levels of significance for the interim and final analyses of OS will be α=0.00305 and α=0.049, respectively.

The final analysis of OS will be completed when 320 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.049 level of significance. The same methodology will be used for the interim analysis, but at the α=0.00305 level of significance.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression. The percentage of subjects with complete or PRs, or stable disease will be evaluated and the disease control rate (CR, PR and SD at 4 months) will be compared using Pearson's chi-square test, or if 20% or more of the expected cell frequencies are <5, Fisher's exact test. Patient reported outcomes as assessed by the EORTC Quality of Life Questionnaire will be analyzed using analysis of covariance.

Sample Size Justification:
Power calculations and subject numbers were calculated based on the primary endpoint of PFS. Reviewing the literature for studies that have evaluated gemcitabine + docetaxel, pazopanib, ifosfamide and dacarbazine as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the investigator's choice group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 5.6 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 191 PFS events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 15 month follow-up period after enrollment of the last subject, approximately 400 subjects will be needed to achieve the total of 191 PFS events.

Safety:
The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Pharmacokinetics: All subjects who receive aldoxorubicin and provide at least one PK sample with concentrations above the limit of quantification will be included in the PK analysis. Sparse plasma aldoxorubicin, doxorubicin, and doxorubicinol concentration data will be analyzed, and aldoxorubicin, doxorubicin, and doxorubicinol PK parameters will be estimated based on a population PK analysis. PK parameters will be summarized using descriptive statistics. Exploratory exposure-response/exposure-safety analyses will be conducted using the primary and secondary efficacy endpoints, PFS and OS, and for selected AEs.	

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -28 Days	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Day 15 and 21 each Cycle	End of Treatment[14]	Every 6 Weeks → Week 30[13]	Every 12 Weeks[13]	Follow Up[12]
Signed informed consent	X													
Review inclusion/exclusion	X	X												
Medical history[1]	X													
Physical examination[22]	X	X	X	X	X	X	X	X	X		X	X	X	
Height (cm)[2]	X	X												
Weight (kg)	X	X	X	X	X	X	X	X	X					
BSA calculation[2]		X	X	X	X	X	X	X	X					
Vital signs[3]	X	X	X	X	X	X	X	X	X		X	X	X	
ECOG PS	X	X	X	X	X	X	X	X	X		X			
CT/ MRI scan / tumor measurements[4]	X[8a]			X[8]		X[8]		X[8]			X[10]	X	X	
ECG[20]	X	X	X	X	X	X	X	X	X		X[11]	X	X	
ECHO (with ejection fraction)[21]	X		X		X		X		X		X	X	X	
CBC w/differential & plts[5]	X	X[16]	X	X	X	X	X	X	X	X	X[11]	X	X	
Serum chemistries[5, 6]	X	X[16]	X	X	X	X	X	X	X	X	X[11]			
Urinalysis[7]	X										X[11]			
Serum/urine pregnancy test	X													
Quality of Life Questionnaire	X				X						X			
Randomization		X[15]												
Aldoxorubicin, doxorubicin, ifosfamide or dacarbazine administration[17]		X	X	X	X	X	X	X	X					
Gemcitabine and docetaxel administration[, 18]		X	X	X	X	X	X	X	X					
Pazopanib administration and diary[19]		X	X	X	X	X	X	X			X			
Pharmacokinetic sampling[23]		X												
Concomitant medications	X[9]	X	X	X	X	X	X	X	X		X			
Adverse events	X	X	X	X	X	X	X	X	X		X			
Telephone call														X

NOTE: All assessment must be performed within 72 hours of each specified time parameter, except Cycle 1 (see Section 7 for details).

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PROTOCOL NUMBER: **ALDOXORUBICIN-P3-STS-01**

STUDY DRUG: **Aldoxorubicin**

IND NUMBER: **113,695**

EUDRACT NUMBER: **2013-004103-40**

SPONSOR: **CytRx Corporation**
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ORIGINAL PROTOCOL: **April 3, 2013**

AMENDMENT 1: **August 28, 2013**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation (CytRx) prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

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at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CytRx.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt MD

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: January 27, 2014

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator's choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS). **Secondary Objectives:** The secondary objectives of this study are to evaluate the efficacy of aldoxorubicin as measured by OS, safety of aldoxorubicin compared to investigator's choice 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, as well as disease control rate, and tumor response. **Exploratory Objectives:** To determine the pharmacokinetics (PK) of aldoxorubicin, doxorubicin, and doxorubicinol following intravenous (IV) administration of aldoxorubicin, and to evaluate the exposure-response relationships between aldoxorubicin, doxorubicin, and/or doxorubicinol and PFS, OS, selected safety parameters, and quality of life.	
Study Rationale and Significance: Aldoxorubicin (INNO-206; DOXO-EMCH) is a novel prodrug that binds covalently to circulating albumin. 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 antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas who have failed prior chemotherapies have a poor prognosis with PFS of around 2-4.6 months and median OS of approximately 9-12 months. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as ifosfamide, gemcitabine, docetaxel, vinorelbine, dacarbazine, temozolomide, epirubicin, pazopanib and liposomal doxorubicin. However, these regimens can be quite toxic and have not significantly impacted either progression-free or OS in these individuals. Pazopanib, recently approved in the US and Europe, does appear to extend PFS in soft tissue sarcoma patients (except liposarcomas) who have relapsed after receiving prior chemotherapy compared to no treatment, but does not increase OS. Aldoxorubicin may improve upon the activity of doxorubicin without an increase in toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Design and Methodology:

This is a phase 3 open-label study evaluating the efficacy and safety of aldoxorubicin administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs compared to investigator's choice of treatment among 5 different therapies. These therapies include: 1) dacarbazine administered at 1000 mg/m^2 by intravenous infusion (IVI), over 90±15 minutes on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs; 2) pazopanib, 800 mg orally each day until tumor progression or unacceptable toxicity occurs; 3) gemcitabine, 900 mg/m^2 by IVI over 90 minutes on Days 1 and 8, plus docetaxel, 100 mg/m^2 by IVI over 1 hour on Day 8 of a 28 day cycle until tumor progression or unacceptable toxicity occurs; 4) doxorubicin, 75 mg/m^2 by IVI over 5 to 30 minutes every 21 days for a maximum cumulative dose of 550 mg/m^2 or unacceptable toxicity occurs; or 5) ifosfamide 2.0 g/m^2 administered over 2 to 4 hours on Days 1-4 of a 21 day cycle + mesna per standard site administration regimen until tumor progression or unacceptable toxicity occurs. The investigative site must **pre-specify** their choice of treatments for the comparator arm to be used at their site, and no more than 3 treatment regimens may be selected for the comparator arm at each site which must be selected **prior** to the study site initiation visit. Subjects will be randomized 1:1 to receive either aldoxorubicin or investigator's choice of up to 3 control regimens pre-selected by the study site. Pretreatment with G-CSF is permitted according to ASCO Guidelines (Appendix E).

All Screening requirements, including an ECHO exam, must be completed within 28 days of the Cycle 1-Day 1 visit. Subjects receiving aldoxorubicin, ifosfamide, dacarbazine or doxorubicin will visit the study site on Day 1 of each cycle. They will have complete blood counts (CBC) and serum chemistries on Day 15 and Day 21 (if Day 21 does not correspond to Day 1 of the next cycle, ±3 days; Day 28 for subjects taking pazopanib) of each cycle as well. Subjects receiving pazopanib will visit the study site on Day 1 of their next cycle for monitoring, testing (same as for Day 1 for other treatment regimens) and to receive a new supply of study drug. Subjects receiving gemcitabine plus docetaxel will visit the study site on both days of their infusions (Days 1 and 8) and at Day 21 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, CBC, and urinalysis), vital signs, weight measurements, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and ECGs will be performed on Day 1 (for all subjects) of each cycle. Cardiac function will also be followed periodically (per Schedule of Treatment and Evaluations in Appendix A) with ECHOs for subjects receiving either aldoxorubicin or doxorubicin. Treatment will continue until tumor progression is observed, a maximum cumulative dose of 550 mg/m^2 is reached (doxorubicin), subject asks to withdraw, unacceptable toxicity occurs, a change in therapy would be in the best interest of the subject, subject becomes pregnant or fails to use adequate birth control, need for any treatment not allowed by the protocol, or subject is non-compliant with study requirements.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[50] OS, PFS, and PFS at 4 and 6 months will be evaluated. Objective overall response rate (ORR) (complete and partial responses [PRs]), disease control rate (objective responses plus stable disease at 4 months) and quality of life will be assessed.

The PK of aldoxorubicin, doxorubicin, and doxorubicinol will be evaluated using a sparse sample analysis. Plasma samples will be collected at Cycle 1 at the following time points: the end of the infusion, between 1.5 and 4 hours from the end of the infusion, and on Days 2, and 3. If necessary and possible, PK samples may be collected at a later cycle.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Has provided written informed consent prior to any study related activities.
2. Age ≥15 years (US only), and 18-80 (rest of world (ROW)), male or female.
3. Histological confirmation of intermediate or high grade soft-tissue sarcoma. Tissue must be sent to a central pathology lab for review but will not preclude entry onto the study. **Final assignment of tumor grade and histology will be based on the designation provided by the central pathology review.**
4. **An adequate tumor specimen obtained by either excisional biopsy, incisional biopsy or core needle biopsy must be sent to the central pathology lab for evaluation. The material must measure at least 0.8 × 0.1 cm in size or contain at least 50 tumor cells.**
5. Locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade with evidence of disease progression by either computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinical judgment on or after the last cancer therapy within 6 months prior to randomization.
6. Relapsed or refractory (lack of response) to ≥1 course of systemic therapy regimen(s), excluding adjuvant or neoadjuvant chemotherapy, and is incurable by either surgery or radiation.
7. Capable of providing informed consent and complying with trial procedures.
8. ECOG PS 0-2.
9. Life expectancy >12 weeks.
10. Measurable tumor lesions according to RECIST 1.1 criteria.[50]
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. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 11 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and agree to continue use for 6 months after the final dose of study treatment.
13. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
14. Accessibility to the site that optimizes the subject's ability to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Palliative surgery and/or radiation treatment within 30 days prior to date of randomization.
3. Exposure to any investigational agent within 30 days of date of randomization.
4. Exposure to any systemic chemotherapy within 30 days of date of randomization.
5. An inadequate tumor specimen as defined by the central pathologist.
6. Current evidence/diagnosis of alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma (unless transformed to fibrosarcoma), Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas.
7. Evidence of central nervous system (CNS) metastasis who have not received prior definitive therapy for their lesions.
8. History of other malignancies except cured basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma *in situ*, superficial bladder cancer or carcinoma *in situ* of the cervix unless documented free of cancer for ≥5 years.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

9. Laboratory values: Screening serum creatinine >1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, hemoglobin <9 g/dL.
10. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) (Appendix D) guidelines.
11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications.
13. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
14. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
15. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
16. Known history of HIV infection.
17. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals. The Medical Monitor should be contacted for any uncertainties.
18. Major surgery within 30 days prior to date of randomization.
19. Current or past substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
20. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:

Approximately 400 subjects with metastatic, locally advanced or unresectable soft tissue sarcomas who have either not responded to or have progressed after treatment with 1 or more systemic regimens of non-adjuvant chemotherapies will be randomized 1:1 (aldoxorubicin:investigator's choice) at approximately 120 study centers in the US, Europe, Canada, Latin America, Asia and Australia. The randomization will be stratified according to their initial PS (ECOG 0-1 vs 2), whether they had either 1 prior systemic non-adjuvant chemotherapy regimens or >1 prior systemic non-adjuvant chemotherapy regimens and whether they had received prior doxorubicin chemotherapy. Subjects will also be stratified by their histopathological diagnosis as determined by the local site. The four stratification groups will be leiomyosarcomas, liposarcoma, synovial sarcoma, and all other sarcomas.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Test Product, Dose and Mode of Administration:

Aldoxorubicin: Lyophilized powder in vials that contain 200 mg of aldoxorubicin reconstituted by adding a solution of 50% ethanol: 50% sterile water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Investigator's Choice: Up to three treatment regimens are to be chosen by the investigator from the list below prior to the initiation of the study site and the treatment chosen for each subject enrolled in the study must be entered into the case report form.

Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, Sterile Water for Injection, USP. The resulting solution contains 10 mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously. The reconstituted solution may be further diluted with 5% dextrose injection, or sodium chloride injection (250 to 500 mL), and administered as an IVI over 90±15 minutes.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Pazopanib (Votrient®) 200 mg tablets can be stored at room temperature between 20° and 25°C; excursions are permitted between 15° and 30°C. Tablets are taken 1 hour before or 2 hours after a meal and tablets are NOT to be crushed.

Gemcitabine 200 mg or 1 g lyophilized powder in a single use vial is reconstituted with 0.9% NaCl to a final concentration of ≤40 mg/mL and pH 2.7 to 3.3. The reconstituted solution may be further diluted with 0.9% NaCl and administered by IVI in <60 minutes. It is stable for up to 24 hours at controlled room temperature
(20° to 25°C) and should not be refrigerated.

Docetaxel 80 mg/2 mL and 20 mg/0.5 mL with diluents for both strengths (13% [w/w] ethanol in water for injection) is administered by IVI over approximately 60 minutes after dilution into a 250 to 500 mL infusion bag of either 0.9% NaCl or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. Docetaxel final dilution for infusion should be administered within 4 hours of preparation. It can be stored between 2° and 25°C.

Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose and may be administered over 5 to 30 minutes.

Ifosamide single-dose vials for constitution and administration by IVI each contain 1 gram or 3 grams of sterile ifosfamide, USP. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Sterile Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved) to the vial and shaking to dissolve. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose solution and may be administered over 2 to 4 hours.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Criteria for Evaluation:

Efficacy:

The following efficacy variables will be evaluated as noted:

- PFS.
- OS.
- Objective tumor response (RECIST 1.1 criteria[50]).
- Disease control rate (objective tumor response + stable disease at 4 months).
- Subject Reported Outcome as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire.

Safety:

The following safety variables will be assessed over the duration 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.

Pharmacokinetics:

The following PK variables will be assessed for aldoxorubicin, doxorubicin, and doxorubicinol:

- Maximum drug concentration (C_{max}) in plasma.
- Area under the plasma drug-concentration-time profile (AUC).
- Clearance (CL).
- Volume of distribution (V_d).
- Half-life ($t_{½}$).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects will be evaluated for efficacy. All subjects who receive at least 1 dose of study medication will be evaluated for safety.

Efficacy:
The primary analysis of PFS will be carried out when approximately 191 PFS events have been observed (approximately 15 months following the completion of enrollment of 400 subjects). Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

An important secondary endpoint is overall survival (OS). The analysis of OS will be considered confirmatory only if the PFS analysis is statistically significant. As a result, the nominal level of significance for the OS analysis will be α=0.05. However, because an interim analysis of OS will be carried out at the time of the analysis of PFS, the levels of significance for the interim and final analyses of OS will be α=0.00305 and α=0.049, respectively.

The final analysis of OS will be completed when 320 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.049 level of significance. The same methodology will be used for the interim analysis, but at the α=0.00305 level of significance.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression. The percentage of subjects with complete or PRs, or stable disease will be evaluated and the disease control rate (CR, PR and SD at 4 months) will be compared using Pearson's chi-square test, or if 20% or more of the expected cell frequencies are <5, Fisher's exact test. Patient reported outcomes as assessed by the EORTC Quality of Life Questionnaire will be analyzed using analysis of covariance.

Sample Size Justification:
Power calculations and subject numbers were calculated based on the primary endpoint of PFS. Reviewing the literature for studies that have evaluated gemcitabine + docetaxel, pazopanib, ifosfamide and dacarbazine as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the investigator's choice group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 5.6 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 191 PFS events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 15 month follow-up period after enrollment of the last subject, approximately 400 subjects will be needed to achieve the total of 191 PFS events.

Safety:
The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Pharmacokinetics: All subjects who receive aldoxorubicin and provide at least one PK sample with concentrations above the limit of quantification will be included in the PK analysis. Sparse plasma aldoxorubicin, doxorubicin, and doxorubicinol concentration data will be analyzed, and aldoxorubicin, doxorubicin, and doxorubicinol PK parameters will be estimated based on a population PK analysis. PK parameters will be summarized using descriptive statistics. Exploratory exposure-response/exposure-safety analyses will be conducted using the primary and secondary efficacy endpoints, PFS and OS, and for selected AEs.	

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8, 9+	Day 15 and 21 each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
GENERAL AND SAFETY														
Informed Consent	X													
Review Inclusion/Exclusion	X	X												
Tumor Specimen[1]	X													
Randomization[2]		X												
Medical History[3]	X													
Physical Examination[4]	X	X	X	X	X	X	X	X	X		X[25]	X[25]	X[25]	
Height (cm)	X	X[5]												
Weight (kg)	X	X	X	X	X	X	X	X	X					
BSA Calculation[5]		X	X	X	X	X	X	X	X					
Vital Signs[6]	X	X	X	X	X	X	X	X	X		X	X	X	
Adverse Events[7]	X	X	X	X	X	X	X	X	X		X			
Survival Follow-Up[8]														X
ECOG PS	X	X	X	X	X	X	X	X	X		X			
Concomitant Medications	X[9]	X	X	X	X	X	X	X	X		X			
RADIOGRAPHIC ASSESSMENTS														
CT/ MRI Scan / Tumor Measurements[10]	X[11a]			X[11]		X[11]		X[11]			X[26]	X	X	
CARDIAC ASSESSMENTS														
ECG[12]	X	X	X	X	X	X	X	X	X		X[27]	X	X	
ECHO (with ejection fraction)[13]	X		X		X		X		X		X	X	X	
CENTRAL LAB ASSESSMENTS														
CBC w/differential & Platelets[14]	X	X[16]	X	X	X	X	X	X	X	X	X[27]	X	X	
Serum Chemistries[14, 15]	X	X[16]	X	X	X	X	X	X	X	X	X[27]			
Pharmacokinetic Sampling[18]		X												
Urinalysis[17]	X										X[27]			
Serum/Urine Pregnancy Test	X													

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8, 9+	Day 15 and 21 each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
LOCAL LAB ASSESSMENTS[28]														
CBC w/differential & Platelets[14]		X[16]	X	X	X	X	X	X	X	X				
Serum Chemistries [14, 15]		X[16]	X	X	X	X	X	X	X	X				
QUALITY OF LIFE QUESTIONNAIRE														
EORTC QLQ-C30 Version 3	X				X						X			
CHEMOTHERAPY: ALDOXORUBICIN OR INVESTIGATOR'S CHOICE														
Aldoxorubicin, Doxorubicin, Ifosfamide or Dacarbazine Administration[19]		X	X	X	X	X	X	X	X					
Gemcitabine and Docetaxel Administration [20]		X	X	X	X	X	X	X	X					
Pazopanib Administration and Diary[21]		X	X	X	X	X	X	X	X					

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

CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy**

PROTOCOL NUMBER: **ALDOXORUBICIN-P3-STS-01**

STUDY DRUG: **Aldoxorubicin**

IND NUMBER: **113,695**

EUDRACT NUMBER: **2013-004103-40**

SPONSOR: **CytRx Corporation**
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ORIGINAL PROTOCOL: **April 3, 2013**
AMENDMENT 1: **August 28, 2013**
AMENDMENT 2: **March 21, 2014**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation (CytRx) prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partner] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CytRx.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: March 25, 2014

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator's choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS). **Secondary Objectives:** The secondary objectives of this study are to evaluate the efficacy of aldoxorubicin as measured by OS, safety of aldoxorubicin compared to investigator's choice 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, as well as disease control rate, and tumor response. **Exploratory Objectives:** To determine the pharmacokinetics (PK) of aldoxorubicin, doxorubicin, and doxorubicinol following intravenous (IV) administration of aldoxorubicin, and to evaluate the exposure-response relationships between aldoxorubicin, doxorubicin, and/or doxorubicinol and PFS, OS, selected safety parameters, and quality of life.	
Study Rationale and Significance: Aldoxorubicin (INNO-206; DOXO-EMCH) is a novel prodrug that binds covalently to circulating albumin. 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 antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas who have failed prior chemotherapies have a poor prognosis with PFS of around 2-4.6 months and median OS of approximately 9-12 months. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as ifosfamide, gemcitabine, docetaxel, vinorelbine, dacarbazine, temozolomide, epirubicin, pazopanib and liposomal doxorubicin. However, these regimens can be quite toxic and have not significantly impacted either progression-free or OS in these individuals. Pazopanib, recently approved in the US and Europe, does appear to extend PFS in soft tissue sarcoma patients (except liposarcomas) who have relapsed after receiving prior chemotherapy compared to no treatment, but does not increase OS. Aldoxorubicin may improve upon the activity of doxorubicin without an increase in toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Design and Methodology:

This is a phase 3 open-label study evaluating the efficacy and safety of aldoxorubicin administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs compared to investigator's choice of treatment among 5 different therapies. These therapies include: 1) dacarbazine administered at 1000 mg/m^2 by intravenous infusion (IVI), over 90±15 minutes on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs; 2) pazopanib, 800 mg orally each day until tumor progression or unacceptable toxicity occurs; 3) gemcitabine, 900 mg/m^2 by IVI in less than 60 minutes on Days 1 and 8, plus docetaxel, 100 mg/m^2 by IVI over 1 hour on Day 8 of a 21 day cycle until tumor progression or unacceptable toxicity occurs; 4) doxorubicin, 75 mg/m^2 by IVI over 5 to 30 minutes every 21 days for a maximum cumulative dose of 550 mg/m^2 or unacceptable toxicity occurs; or 5) ifosfamide 2.0 g/m^2 administered over 2 to 4 hours on Days 1-4 of a 21 day cycle + mesna per standard site administration regimen until tumor progression or unacceptable toxicity occurs. The investigative site must **pre-specify** their choice of treatments for the comparator arm to be used at their site, and no more than 3 treatment regimens may be selected for the comparator arm at each site which must be selected **prior** to the study site initiation visit. Subjects will be randomized 1:1 to receive either aldoxorubicin or investigator's choice of up to 3 control regimens pre-selected by the study site. Pretreatment with G-CSF is permitted according to ASCO Guidelines (Appendix E).

All Screening requirements, including an ECHO exam, must be completed within 28 days of the Cycle 1-Day 1 visit. Subjects receiving aldoxorubicin, ifosfamide, dacarbazine or doxorubicin will visit the study site on Day 1 of each cycle. They will have complete blood counts (CBC) and serum chemistries on Day 15 and Day 21 (if Day 21 does not correspond to Day 1 of the next cycle, ±3 days) of each cycle as well. Subjects receiving pazopanib will visit the study site on Day 1 of their next cycle for monitoring, testing (same as for Day 1 for other treatment regimens) and to receive a new supply of study drug. Subjects receiving pazopanib will also have CBC and serum chemistry on Day 15 and Day 28 (if Day 28 does not correspond to Day 1 of the next cycle, ±2 days). Subjects receiving gemcitabine plus docetaxel will visit the study site on both days of their infusions (Days 1 and 8) and at Days 15 and 21 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, CBC, and urinalysis), vital signs, weight measurements, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and ECGs will be performed on Day 1 (for all subjects) of each cycle. Cardiac function will also be followed periodically (per Schedule of Treatment and Evaluations in Appendix A) with ECHOs for subjects receiving either aldoxorubicin or doxorubicin. Treatment will continue until tumor progression is observed, a maximum cumulative dose of 550 mg/m^2 is reached (doxorubicin), subject asks to withdraw, unacceptable toxicity occurs, a change in therapy would be in the best interest of the subject, subject becomes pregnant or fails to use adequate birth control, need for any treatment not allowed by the protocol, or subject is non-compliant with study requirements.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[50] OS, PFS, and PFS at 4 and 6 months will be evaluated. Objective overall response rate (ORR) (complete and partial responses [PRs]), disease control rate (objective responses plus stable disease at 4 months) and quality of life will be assessed.

The PK of aldoxorubicin, doxorubicin, and doxorubicinol will be evaluated using a sparse sample analysis. Plasma samples will be collected at Cycle 1 at the following time points: the end of the infusion, between 1.5 and 4 hours from the end of the infusion, and on Days 2, and 3. If necessary and possible, PK samples may be collected at a later cycle.

Name of Sponsor/Company: CytRx Corporation

Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Has provided written informed consent prior to any study related activities.
2. Age ≥15 years (US only), and 18-80 (rest of world (ROW)), male or female.
3. Histological confirmation of intermediate or high grade soft-tissue sarcoma. Tissue must be sent to a central pathology lab for review but will not preclude entry onto the study. **Final assignment of tumor grade and histology will be based on the designation provided by the central pathology review.**
4. **An adequate tumor specimen obtained by either excisional biopsy, incisional biopsy or core needle biopsy must be sent to the central pathology lab for evaluation. The material must measure at least 0.8 × 0.1 cm in size or contain at least 50 tumor cells.**
5. Locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade with evidence of disease progression by either computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinical judgment on or after the last cancer therapy within 6 months prior to randomization.
6. Relapsed or refractory (lack of response) to ≥1 course of systemic therapy regimen(s), excluding adjuvant or neoadjuvant chemotherapy, and is incurable by either surgery or radiation.
7. Capable of providing informed consent and complying with trial procedures.
8. ECOG PS 0-2.
9. Life expectancy >12 weeks.
10. Measurable tumor lesions according to RECIST 1.1 criteria.[50]
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. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 11 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and agree to continue use for 6 months after the final dose of study treatment.
13. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
14. Accessibility to the site that optimizes the subject's ability to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Palliative surgery and/or radiation treatment within 30 days prior to date of randomization.
3. Exposure to any investigational agent within 30 days of date of randomization.
4. Exposure to any systemic chemotherapy within 30 days of date of randomization.
5. An inadequate tumor specimen as defined by the central pathologist.
6. Current evidence/diagnosis of alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma (unless transformed to fibrosarcoma), Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas.
7. Evidence of central nervous system (CNS) metastasis who have not received prior definitive therapy for their lesions.
8. History of other malignancies except cured basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma *in situ*, superficial bladder cancer or carcinoma *in situ* of the cervix unless documented free of cancer for ≥5 years.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

9. Laboratory values: Screening serum creatinine >1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, hemoglobin <9 g/dL.
10. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) (Appendix D) guidelines.
11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications.
13. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
14. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
15. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
16. Known history of HIV infection.
17. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals. The Medical Monitor should be contacted for any uncertainties.
18. Major surgery within 30 days prior to date of randomization.
19. Current or past substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
20. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:

Approximately 400 subjects with metastatic, locally advanced or unresectable soft tissue sarcomas who have either not responded to or have progressed after treatment with 1 or more systemic regimens of non-adjuvant chemotherapies will be randomized 1:1 (aldoxorubicin:investigator's choice) at approximately 120 study centers in the US, Europe, Canada, Latin America, Asia and Australia. The randomization will be stratified according to their initial PS (ECOG 0-1 vs 2), whether they had either 1 prior systemic non-adjuvant chemotherapy regimens or >1 prior systemic non-adjuvant chemotherapy regimens and whether they had received prior doxorubicin chemotherapy. Subjects will also be stratified by their histopathological diagnosis as determined by the local site. The four stratification groups will be leiomyosarcomas, liposarcoma, synovial sarcoma, and all other sarcomas.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Test Product, Dose and Mode of Administration:

Aldoxorubicin: Lyophilized powder in vials that contain 200 mg of aldoxorubicin reconstituted by adding a solution of 50% ethanol: 50% sterile water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Investigator's Choice: Up to three treatment regimens are to be chosen by the investigator from the list below prior to the initiation of the study site and the treatment chosen for each subject enrolled in the study must be entered into the case report form.

Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, Sterile Water for Injection, USP. The resulting solution contains 10 mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously. The reconstituted solution may be further diluted with 5% dextrose injection, or sodium chloride injection (250 to 500 mL), and administered as an IVI over 90±15 minutes.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Pazopanib (Votrient®) 200 mg tablets can be stored at room temperature between 20° and 25°C; excursions are permitted between 15° and 30°C. Tablets are taken 1 hour before or 2 hours after a meal and tablets are NOT to be crushed.

Gemcitabine 200 mg or 1 g lyophilized powder in a single use vial is reconstituted with 0.9% NaCl to a final concentration of ≤40 mg/mL and pH 2.7 to 3.3. The reconstituted solution may be further diluted with 0.9% NaCl and administered by IVI in <60 minutes. It is stable for up to 24 hours at controlled room temperature (20° to 25°C) and should not be refrigerated.

Docetaxel 80 mg/2 mL and 20 mg/0.5 mL with diluents for both strengths (13% [w/w] ethanol in water for injection) is administered by IVI over approximately 60 minutes after dilution into a 250 to 500 mL infusion bag of either 0.9% NaCl or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. Docetaxel final dilution for infusion should be administered within 4 hours of preparation. It can be stored between 2° and 25°C.

Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose and may be administered over 5 to 30 minutes.

Ifosamide single-dose vials for constitution and administration by IVI each contain 1 gram or 3 grams of sterile ifosfamide, USP. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Sterile Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved) to the vial and shaking to dissolve. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose solution and may be administered over 2 to 4 hours.

See Section 5.2 for additional investigator's choice treatment concentrations and preparation instructions as per package inserts.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Criteria for Evaluation:

Efficacy:

The following efficacy variables will be evaluated as noted:

- PFS.
- OS.
- Objective tumor response (RECIST 1.1 criteria[50]).
- Disease control rate (objective tumor response + stable disease at 4 months).
- Subject Reported Outcome as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire.

Safety:

The following safety variables will be assessed over the duration 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.

Pharmacokinetics:

The following PK variables will be assessed for aldoxorubicin, doxorubicin, and doxorubicinol:

- Maximum drug concentration (C_{max}) in plasma.
- Area under the plasma drug-concentration-time profile (AUC).
- Clearance (CL).
- Volume of distribution (V_d).
- Half-life ($t_{½}$).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects will be evaluated for efficacy. All subjects who receive at least 1 dose of study medication will be evaluated for safety.

Efficacy:
The primary analysis of PFS will be carried out when approximately 191 PFS events have been observed (approximately 15 months following the completion of enrollment of 400 subjects). Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

An important secondary endpoint is overall survival (OS). The analysis of OS will be considered confirmatory only if the PFS analysis is statistically significant. As a result, the nominal level of significance for the OS analysis will be α=0.05. However, because an interim analysis of OS will be carried out at the time of the analysis of PFS, the levels of significance for the interim and final analyses of OS will be α=0.00305 and α=0.049, respectively.

The final analysis of OS will be completed when 320 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.049 level of significance. The same methodology will be used for the interim analysis, but at the α=0.00305 level of significance.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression. The percentage of subjects with complete or PRs, or stable disease will be evaluated and the disease control rate (CR, PR and SD at 4 months) will be compared using Pearson's chi-square test, or if 20% or more of the expected cell frequencies are <5, Fisher's exact test. Patient reported outcomes as assessed by the EORTC Quality of Life Questionnaire will be analyzed using analysis of covariance.

Sample Size Justification:
Power calculations and subject numbers were calculated based on the primary endpoint of PFS. Reviewing the literature for studies that have evaluated gemcitabine + docetaxel, pazopanib, ifosfamide and dacarbazine as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the investigator's choice group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 5.6 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 191 PFS events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 15 month follow-up period after enrollment of the last subject, approximately 400 subjects will be needed to achieve the total of 191 PFS events.

Safety:
The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Pharmacokinetics: All subjects who receive aldoxorubicin and provide at least one PK sample with concentrations above the limit of quantification will be included in the PK analysis. Sparse plasma aldoxorubicin, doxorubicin, and doxorubicinol concentration data will be analyzed, and aldoxorubicin, doxorubicin, and doxorubicinol PK parameters will be estimated based on a population PK analysis. PK parameters will be summarized using descriptive statistics. Exploratory exposure-response/exposure-safety analyses will be conducted using the primary and secondary efficacy endpoints, PFS and OS, and for selected AEs.	

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8, 9+	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
GENERAL AND SAFETY														
Informed Consent	X													
Review Inclusion/Exclusion	X	X												
Tumor Specimen[1]	X													
Randomization[2]		X												
Medical History[3]	X													
Physical Examination[4]	X	X	X	X	X	X	X	X	X		X[25]	X[25]	X[25]	
Height (cm)	X	X[5]												
Weight (kg)	X	X	X	X	X	X	X	X	X					
BSA Calculation[5]		X	X	X	X	X	X	X	X					
Vital Signs[6]	X	X	X	X	X	X	X	X	X		X	X	X	
Adverse Events[7]		X	X	X	X	X	X	X	X		X			
Survival Follow-Up[8]														X
ECOG PS	X	X	X	X	X	X	X	X	X		X			
Concomitant Medications	X[9]	X	X	X	X	X	X	X	X		X			
RADIOGRAPHIC ASSESSMENTS														
CT/ MRI Scan / Tumor Measurements[10]	X[11a]			X[11]		X[11]		X[11]			X[26]	X	X	
CARDIAC ASSESSMENTS														
ECG[12]	X	X	X	X	X	X	X	X	X		X[27]	X	X	
ECHO (with ejection fraction)[13]	X		X		X		X		X		X	X	X	
CENTRAL LAB ASSESSMENTS														
CBC w/differential & Platelets[14]	X	X[16]	X	X	X	X	X	X	X	X	X[27]	X	X	
Serum Chemistries[14, 15]	X	X[16]	X	X	X	X	X	X	X	X	X[27]			
Pharmacokinetic Sampling[18]		X												
Urinalysis[17]	X										X[27]			
Serum/Urine Pregnancy Test	X													

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8, 9+	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
LOCAL LAB ASSESSMENTS[28]														
CBC w/differential & Platelets[14]		X[16]	X	X	X	X	X	X	X	X				
Serum Chemistries [14, 15]		X[16]	X	X	X	X	X	X	X	X				
QUALITY OF LIFE QUESTIONNAIRE														
EORTC QLQ-C30 Version 3	X				X						X			
CHEMOTHERAPY: ALDOXORUBICIN OR INVESTIGATOR'S CHOICE														
Aldoxorubicin, Doxorubicin, Ifosfamide or Dacarbazine Administration[19]		X	X	X	X	X	X	X	X					
Gemcitabine and Docetaxel Administration [20]		X	X	X	X	X	X	X	X					
Pazopanib Administration and Diary[21]		X	X	X	X	X	X	X	X					

NOTE: All assessment must be performed within 72 hours of each specified time parameter (48 hours for pazopanib treated subjects), except Cycle 1 (see Section 6 for details).

CytRx® CORPORATION

CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy**

PROTOCOL NUMBER: **ALDOXORUBICIN-P3-STS-01**

STUDY DRUG: **Aldoxorubicin**

IND NUMBER: **113,695**

EUDRACT NUMBER: **2013-004103-40**

SPONSOR: **CytRx Corporation**
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Europe	+44 1792 52-5608	+49 621 878-2828	AldoxP3STS@PRAIntl.com

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ORIGINAL PROTOCOL: **April 3, 2013**
AMENDMENT 1: **August 28, 2013**
AMENDMENT 2: **March 21, 2014**
AMENDMENT 3: **January 13, 2015**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation (CytRx) prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partner] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CytRx.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: 1-19-2015

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator's choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS). **Secondary Objectives:** The secondary objectives of this study are to evaluate the efficacy of aldoxorubicin as measured by OS, safety of aldoxorubicin compared to investigator's choice 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, as well as disease control rate, and tumor response. **Exploratory Objectives:** To determine the pharmacokinetics (PK) of aldoxorubicin, doxorubicin, and doxorubicinol following intravenous (IV) administration of aldoxorubicin, and to evaluate the exposure-response relationships between aldoxorubicin, doxorubicin, and/or doxorubicinol and PFS, OS, selected safety parameters, and quality of life.	
Study Rationale and Significance: Aldoxorubicin (INNO-206; DOXO-EMCH) is a novel prodrug that binds covalently to circulating albumin. 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 antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas who have failed prior chemotherapies have a poor prognosis with PFS of around 2-4.6 months and median OS of approximately 9-12 months. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as ifosfamide, gemcitabine, docetaxel, vinorelbine, dacarbazine, temozolomide, epirubicin, pazopanib and liposomal doxorubicin. However, these regimens can be quite toxic and have not significantly impacted either progression-free or OS in these individuals. Pazopanib, recently approved in the US and Europe, does appear to extend PFS in soft tissue sarcoma patients (except liposarcomas) who have relapsed after receiving prior chemotherapy compared to no treatment, but does not increase OS. Aldoxorubicin may improve upon the activity of doxorubicin without an increase in toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Design and Methodology:

This is a phase 3 open-label study evaluating the efficacy and safety of aldoxorubicin administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs compared to investigator's choice of treatment among 5 different therapies. These therapies include (dosages should follow the institutional standard of care, package insert (SPCs), or the following suggestions based on the US package inserts and the literature): 1) dacarbazine administered at 1000 mg/m^2 by intravenous infusion (IVI), over 90±15 minutes on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs; 2) pazopanib, 800 mg orally each day until tumor progression or unacceptable toxicity occurs; 3) gemcitabine, 900 mg/m^2 by IVI in less than 60 minutes on Days 1 and 8, plus docetaxel, 100 mg/m^2 by IVI over 1 hour on Day 8 of a 21 day cycle until tumor progression or unacceptable toxicity occurs; 4) doxorubicin, 75 mg/m^2 by IVI over 5 to 30 minutes every 21 days for a maximum cumulative dose of 550 mg/m^2 or unacceptable toxicity occurs; or 5) ifosfamide 2.0 g/m^2 administered over 2 to 4 hours on Days 1-4 of a 21 day cycle + mesna per standard site administration regimen until tumor progression or unacceptable toxicity occurs. The investigative site must **pre-specify** their choice of treatments for the comparator arm to be used at their site, and no more than 3 treatment regimens may be selected for the comparator arm at each site which must be selected **prior** to the study site initiation visit. Subjects will be randomized 1:1 to receive either aldoxorubicin or investigator's choice of up to 3 control regimens pre-selected by the study site. Treatment with G-CSF should be administered to all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E). **Note: aldoxorubicin has been associated with >20% incidence of grade 3 or 4 neutropenia. Therefore, the administration of G-CSF should occur even during Cycle 1.**

All Screening requirements, including an ECHO exam, must be completed within 28 days of the Cycle 1-Day 1 visit. Subjects receiving aldoxorubicin, ifosfamide, dacarbazine or doxorubicin will visit the study site on Day 1 of each cycle. They will have complete blood counts (CBC) and serum chemistries on Day 15 and Day 21 (if Day 21 does not correspond to Day 1 of the next cycle, ±3 days) of each cycle as well. Subjects receiving pazopanib will visit the study site on Day 1 of their next cycle for monitoring, testing (same as for Day 1 for other treatment regimens) and to receive a new supply of study drug. Subjects receiving pazopanib will also have CBC and serum chemistry on Day 15 and Day 28 (if Day 28 does not correspond to Day 1 of the next cycle, ±2 days). Subjects receiving gemcitabine plus docetaxel will visit the study site on both days of their infusions (Days 1 and 8) and at Days 15 and 21 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, CBC, and urinalysis), vital signs, weight measurements, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and ECGs will be performed on Day 1 (for all subjects) of each cycle. Subjects receiving aldoxorubicin will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically (per Schedule of Treatment and Evaluations in Appendix A) with ECHOs for subjects receiving either aldoxorubicin or doxorubicin. Treatment will continue until tumor progression is observed, a maximum cumulative dose of 550 mg/m^2 is reached (doxorubicin), subject asks to withdraw, unacceptable toxicity occurs, a change in therapy would be in the best interest of the subject, subject becomes pregnant or fails to use adequate birth control, need for any treatment not allowed by the protocol, or subject is non-compliant with study requirements.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[50] OS, PFS, and PFS at 4 and 6 months will be evaluated. Objective overall response rate (ORR) (complete and partial responses [PRs]), disease control rate (objective responses plus stable disease at 4 months) and quality of life will be assessed.

The PK of aldoxorubicin, doxorubicin, and doxorubicinol will be evaluated using a sparse sample analysis. Plasma samples will be collected at Cycle 1 at the following time points: the end of the infusion, between 1.5 and 4 hours from the end of the infusion, and on Days 2, and 3. If necessary and possible, PK samples may be collected at a later cycle.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Has provided written informed consent prior to any study related activities.
2. Age ≥15 years (US only), and 18-80 (rest of world (ROW)), male or female.
3. Histological confirmation of intermediate or high grade soft-tissue sarcoma as determined by the local pathology report. Archival tissue must be sent to a central pathology lab for review but will not preclude entry onto the study (study-specific biopsies are not allowed). **Final assignment of tumor grade and histology will be based on the designation provided by the central pathology review.**
4. **An adequate tumor specimen obtained by either excisional biopsy, incisional biopsy or core needle biopsy must be sent to the central pathology lab for evaluation.**
5. Locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade with evidence of disease progression by either computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinical judgment on or after the last cancer therapy within 6 months prior to randomization.
6. Relapsed or refractory (lack of response) to ≥1 course of systemic therapy regimen(s), excluding adjuvant or neoadjuvant chemotherapy, and is incurable by either surgery or radiation.
7. Capable of providing informed consent and complying with trial procedures.
8. ECOG PS 0-2.
9. Life expectancy >12 weeks.
10. Measurable tumor lesions according to RECIST 1.1 criteria.[50]
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. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 11 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and agree to continue use for 6 months after the final dose of study treatment.
13. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
14. Accessibility to the site that optimizes the subject's ability to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Palliative surgery and/or radiation treatment within 30 days prior to date of randomization.
3. Exposure to any investigational agent within 30 days of date of randomization.
4. Exposure to any systemic chemotherapy within 30 days of date of randomization.
5. An inadequate tumor specimen as defined by the central pathologist.
6. Current evidence/diagnosis of alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma (unless transformed to fibrosarcoma), Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas.
7. Evidence of central nervous system (CNS) metastasis who have not received prior definitive therapy for their lesions.
8. History of other malignancies except cured basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma *in situ*, superficial bladder cancer or carcinoma *in situ* of the cervix unless documented free of cancer for ≥5 years.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

9. Laboratory values: Screening serum creatinine >1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, hemoglobin <9 g/dL.
10. Anion gap > 16 meq/L (Central Laboratory) or arterial blood pH < 7.30 (as determined by the Local Laboratory).
11. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) (Appendix D) guidelines.
12. 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 F).
13. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications.
14. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
15. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
16. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
17. Known history of HIV infection.
18. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals. The Medical Monitor should be contacted for any uncertainties.
19. Major surgery within 30 days prior to date of randomization.
20. Current or past substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
21. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:

Approximately 400 subjects with metastatic, locally advanced or unresectable soft tissue sarcomas who have either not responded to or have progressed after treatment with 1 or more systemic regimens of non-adjuvant chemotherapies will be randomized 1:1 (aldoxorubicin:investigator's choice) at approximately 120 study centers in the US, Europe, Canada, Latin America, and Australia. The randomization will be stratified according to their initial PS (ECOG 0-1 vs 2), whether they had either 1 prior systemic non-adjuvant chemotherapy regimens or >1 prior systemic non-adjuvant chemotherapy regimens and whether they had received prior doxorubicin chemotherapy. Subjects will also be stratified by their histopathological diagnosis as determined by the local site. The four stratification groups will be leiomyosarcomas, liposarcoma, synovial sarcoma, and all other sarcomas.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Test Product, Dose and Mode of Administration:

Aldoxorubicin: Lyophilized powder in vials that contain 200 mg of aldoxorubicin reconstituted by adding a solution of 50% ethanol: 50% sterile water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent). Aldoxorubicin infusion may exceed 30 minutes if deemed necessary by the investigative site but the total time from the completion of reconstitution of aldoxorubicin to completion of infusion must not be more than 2 hours.

Investigator's Choice: Up to three treatment regimens are to be chosen by the investigator from the list below prior to the initiation of the study site and the treatment chosen for each subject enrolled in the study must be entered into the case report form. Directions for dosage and reconstitution should follow institutional standard of care, package inserts (SPCs), or the suggestions below based on the US package inserts and the literature.

Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, Sterile Water for Injection, USP. The resulting solution contains 10 mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously. The reconstituted solution may be further diluted with 5% dextrose injection, or sodium chloride injection (250 to 500 mL), and administered as an IVI over 90±15 minutes.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Pazopanib (Votrient®) 200 mg tablets can be stored at room temperature between 20° and 25°C; excursions are permitted between 15° and 30°C. Tablets are taken 1 hour before or 2 hours after a meal and tablets are NOT to be crushed.

Gemcitabine 200 mg or 1 g lyophilized powder in a single use vial is reconstituted with 0.9% NaCl to a final concentration of ≤40 mg/mL and pH 2.7 to 3.3. The reconstituted solution may be further diluted with 0.9% NaCl and administered by IVI in <60 minutes. It is stable for up to 24 hours at controlled room temperature (20° to 25°C) and should not be refrigerated.

Docetaxel 80 mg/8 mL and 20 mg/2 mL is administered by IVI over approximately 60 minutes after dilution into a 250 to 500 mL infusion bag of either 0.9% NaCl or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. Docetaxel final dilution for infusion should be administered within 4 hours of preparation. It can be stored between 2° and 25°C.

Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose and may be administered over 5 to 30 minutes.

Ifosamide single-dose vials for constitution and administration by IVI each contain 1 gram or 3 grams of sterile ifosfamide, USP. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Sterile Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved) to the vial and shaking to dissolve. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose solution and may be administered over 2 to 4 hours.

See Section 5.2 for additional investigator's choice treatment concentrations and preparation instructions as per package inserts.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Criteria for Evaluation:

Efficacy:

The following efficacy variables will be evaluated as noted:

- PFS.
- OS.
- Objective tumor response (RECIST 1.1 criteria[50]).
- Disease control rate (objective tumor response + stable disease at 4 months).
- Subject Reported Outcome as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire.

Safety:

The following safety variables will be assessed over the duration 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.

Pharmacokinetics:

The following PK variables will be assessed for aldoxorubicin, doxorubicin, and doxorubicinol:

- Maximum drug concentration (C_{max}) in plasma.
- Area under the plasma drug-concentration-time profile (AUC).
- Clearance (CL).
- Volume of distribution (V_d).
- Half-life ($t_{½}$).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects will be evaluated for efficacy. All subjects who receive at least 1 dose of study medication will be evaluated for safety.

Efficacy:
The primary analysis of PFS will be carried out when approximately 191 PFS events have been observed by the blinded Central Imaging Research Organization (approximately 15 months following the completion of enrollment of 400 subjects). Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

An important secondary endpoint is overall survival (OS). The analysis of OS will be considered confirmatory only if the PFS analysis is statistically significant. As a result, the nominal level of significance for the OS analysis will be α=0.05. However, because an interim analysis of OS will be carried out at the time of the analysis of PFS, the levels of significance for the interim and final analyses of OS will be α=0.00305 and α=0.049, respectively.

The final analysis of OS will be completed when 320 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.049 level of significance. The same methodology will be used for the interim analysis, but at the α=0.00305 level of significance.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression. The percentage of subjects with complete or PRs, or stable disease will be evaluated and the disease control rate (CR, PR and SD at 4 months) will be compared using Pearson's chi-square test, or if 20% or more of the expected cell frequencies are <5, Fisher's exact test. Patient reported outcomes as assessed by the EORTC Quality of Life Questionnaire will be analyzed using analysis of covariance.

Sample Size Justification:
Power calculations and subject numbers were calculated based on the primary endpoint of PFS. Reviewing the literature for studies that have evaluated gemcitabine + docetaxel, pazopanib, ifosfamide and dacarbazine as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the investigator's choice group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 5.6 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 191 events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 15 month follow-up period after enrollment of the last subject, approximately 400 subjects will be needed to achieve the total of 191 events.

Safety:
The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Pharmacokinetics: All subjects who receive aldoxorubicin and provide at least one PK sample with concentrations above the limit of quantification will be included in the PK analysis. Sparse plasma aldoxorubicin, doxorubicin, and doxorubicinol concentration data will be analyzed, and aldoxorubicin, doxorubicin, and doxorubicinol PK parameters will be estimated based on a population PK analysis. PK parameters will be summarized using descriptive statistics. Exploratory exposure-response/exposure-safety analyses will be conducted using the primary and secondary efficacy endpoints, PFS and OS, and for selected AEs.	

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3[22]	Cycle 4[22]	Cycle 5[22]	Cycle 6[22]	Cycle 7[22]	Cycle 8[22], 9+[22]	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
GENERAL AND SAFETY														
Informed Consent	X													
Review Inclusion/Exclusion	X	X												
Tumor Specimen[1]	X													
Randomization[2]		X												
Medical History[3]	X													
Physical Examination[4]	X	X	X	X	X	X	X	X	X		X[25]	X[25]	X[25]	
Height (cm)	X	X[5]												
Weight (kg)	X	X	X	X	X	X	X	X	X					
BSA Calculation[5]		X	X	X	X	X	X	X	X					
Vital Signs[6]	X	X	X	X	X	X	X	X	X		X	X	X	
Adverse Events[7]		X	X	X	X	X	X	X	X		X			
Survival Follow-Up[8]														X
ECOG PS	X	X	X	X	X	X	X	X	X		X			
Concomitant Medications	X[9]	X	X	X	X	X	X	X	X		X			
RADIOGRAPHIC ASSESSMENTS														
CT/ MRI Scan / Tumor Measurements[10]	X[11a]			X[11]		X[11]		X[11]				X	X	
CARDIAC ASSESSMENTS														
ECG[12]	X	X	X	X	X	X	X	X	X		X[26]	X	X	
ECHO (with ejection fraction)[13]	X		X		X		X		X		X	X	X	
CENTRAL LAB ASSESSMENTS														
CBC w/differential & Platelets[14]	X	X[16]	X	X	X	X	X	X	X	X	X[26]	X	X	
Serum Chemistries[14, 15]	X	X[16]	X	X	X	X	X	X	X	X	X[26]			
Pharmacokinetic Sampling[18]		X												
Urinalysis[17]	X										X[26]			
Serum/Urine Pregnancy Test	X													

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3[22]	Cycle 4[22]	Cycle 5[22]	Cycle 6[22]	Cycle 7[22]	Cycle 8[22], 9+[22]	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
LOCAL LAB ASSESSMENTS[27]														
CBC w/differential & Platelets[14]	X*	X[16]	X	X	X	X	X	X	X	X				
Serum Chemistries [14, 15]		X[16]	X	X	X	X	X	X	X	X				
QUALITY OF LIFE QUESTIONNAIRE														
EORTC QLQ-C30 Version 3	X				X						X			
CHEMOTHERAPY: ALDOXORUBICIN OR INVESTIGATOR'S CHOICE														
Aldoxorubicin, Doxorubicin, Ifosfamide or Dacarbazine Administration[19]		X	X	X	X	X	X	X	X					
Gemcitabine and Docetaxel Administration [20]		X	X	X	X	X	X	X	X					
Pazopanib Administration and Diary[21]		X	X	X	X	X	X	X	X					

NOTE: All assessment must be performed within 72 hours of each specified time parameter (48 hours for pazopanib treated subjects), except Cycle 1 (see Section 6 for details).

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

CytRx® CORPORATION

CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy**

PROTOCOL NUMBER: **ALDOXORUBICIN-P3-STS-01**

STUDY DRUG: **Aldoxorubicin**

IND NUMBER: **113,695**

EUDRACT NUMBER: **2013-004103-40**

SPONSOR: **CytRx Corporation**
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Europe	+44 1792 52-5608	+49 621 878-2828	AldoxP3STS@PRAIntl.com

SAE SUBMISSION:

Region	SAE Fax	SAE Email
North America	1-888-772-6919	CHOSafety@PRAIntl.com
Rest of World	+44 1792 525-720	MHGSafety@PRAIntl.com

ORIGINAL PROTOCOL: **April 3, 2013**
AMENDMENT 1: **August 28, 2013**
AMENDMENT 2: **March 21, 2014**
AMENDMENT 3: **January 13, 2015**
AMENDMENT 4: **April 13, 2015**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation (CytRx) prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partner] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CytRx.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: July 9, 2015

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator's choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS). **Secondary Objectives:** The secondary objectives of this study are to evaluate the efficacy of aldoxorubicin as measured by OS, safety of aldoxorubicin compared to investigator's choice 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, as well as disease control rate, and tumor response. **Exploratory Objectives:** To determine the pharmacokinetics (PK) of aldoxorubicin, doxorubicin, and doxorubicinol following intravenous (IV) administration of aldoxorubicin, and to evaluate the exposure-response relationships between aldoxorubicin, doxorubicin, and/or doxorubicinol and PFS, OS, selected safety parameters, and quality of life.	
Study Rationale and Significance: Aldoxorubicin (INNO-206; DOXO-EMCH) is a novel prodrug that binds covalently to circulating albumin. 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 antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas who have failed prior chemotherapies have a poor prognosis with PFS of around 2-4.6 months and median OS of approximately 9-12 months. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as ifosfamide, gemcitabine, docetaxel, vinorelbine, dacarbazine, temozolomide, epirubicin, pazopanib and liposomal doxorubicin. However, these regimens can be quite toxic and have not significantly impacted either progression-free or OS in these individuals. Pazopanib, recently approved in the US and Europe, does appear to extend PFS in soft tissue sarcoma patients (except liposarcomas) who have relapsed after receiving prior chemotherapy compared to no treatment, but does not increase OS. Aldoxorubicin may improve upon the activity of doxorubicin without an increase in toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Design and Methodology:

This is a phase 3 open-label study evaluating the efficacy and safety of aldoxorubicin administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs compared to investigator's choice of treatment among 5 different therapies. These therapies include (dosages should follow the institutional standard of care, package insert (SPCs), or the following suggestions based on the US package inserts and the literature): 1) dacarbazine administered at 1000 mg/m^2 by intravenous infusion (IVI), over 90±15 minutes on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs; 2) pazopanib, 800 mg orally each day until tumor progression or unacceptable toxicity occurs; 3) gemcitabine, 900 mg/m^2 by IVI in less than 60 minutes on Days 1 and 8, plus docetaxel, 100 mg/m^2 by IVI over 1 hour on Day 8 of a 21 day cycle until tumor progression or unacceptable toxicity occurs; 4) doxorubicin, 75 mg/m^2 by IVI over 5 to 30 minutes every 21 days for a maximum cumulative dose of 550 mg/m^2 or unacceptable toxicity occurs; or 5) ifosfamide 2.0 g/m^2 administered over 2 to 4 hours on Days 1-4 of a 21 day cycle + mesna per standard site administration regimen until tumor progression or unacceptable toxicity occurs. The investigative site must **pre-specify** their choice of treatments for the comparator arm to be used at their site, and no more than 3 treatment regimens may be selected for the comparator arm at each site which must be selected **prior** to the study site initiation visit. Subjects will be randomized 1:1 to receive either aldoxorubicin or investigator's choice of up to 3 control regimens pre-selected by the study site. Treatment with G-CSF should be administered to all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E). **Note: aldoxorubicin has been associated with >20% incidence of grade 3 or 4 neutropenia. Therefore, the administration of G-CSF should occur even during Cycle 1.**

All Screening requirements, including an ECHO exam, must be completed within 28 days of the Cycle 1-Day 1 visit. Subjects receiving aldoxorubicin, ifosfamide, dacarbazine or doxorubicin will visit the study site on Day 1 of each cycle. They will have complete blood counts (CBC) and serum chemistries on Day 15 and Day 21 (if Day 21 does not correspond to Day 1 of the next cycle, ±3 days) of each cycle as well. Subjects receiving pazopanib will visit the study site on Day 1 of their next cycle for monitoring, testing (same as for Day 1 for other treatment regimens) and to receive a new supply of study drug. Subjects receiving pazopanib will also have CBC and serum chemistry on Day 15 and Day 28 (if Day 28 does not correspond to Day 1 of the next cycle, ±2 days). Subjects receiving gemcitabine plus docetaxel will visit the study site on both days of their infusions (Days 1 and 8) and at Days 15 and 21 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, CBC, and urinalysis), vital signs, weight measurements, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and ECGs will be performed on Day 1 (for all subjects) of each cycle. Subjects receiving aldoxorubicin will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically (per Schedule of Treatment and Evaluations in Appendix A) with ECHOs for subjects receiving either aldoxorubicin or doxorubicin. Treatment will continue until tumor progression is observed, a maximum cumulative dose of 550 mg/m^2 is reached (doxorubicin), subject asks to withdraw, unacceptable toxicity occurs, a change in therapy would be in the best interest of the subject, subject becomes pregnant or fails to use adequate birth control, need for any treatment not allowed by the protocol, or subject is non-compliant with study requirements.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[50] OS, PFS, and PFS at 4 and 6 months will be evaluated. Objective overall response rate (ORR) (complete and partial responses [PRs]), disease control rate (objective responses plus stable disease at 4 months) and quality of life will be assessed.

The PK of aldoxorubicin, doxorubicin, and doxorubicinol will be evaluated using a sparse sample analysis. Plasma samples will be collected at Cycle 1 at the following time points: the end of the infusion, between 1.5 and 4 hours from the end of the infusion, and on Days 2, and 3. If necessary and possible, PK samples may be collected at a later cycle.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Has provided written informed consent prior to any study related activities.
2. Age ≥15 years (US only), and 18-80 (rest of world (ROW)), male or female.
3. Histological confirmation of intermediate or high grade soft-tissue sarcoma as determined by the local pathology report. Archival tissue must be sent to a central pathology lab for review but will not preclude entry onto the study (study-specific biopsies are not allowed). **Final assignment of tumor grade and histology will be based on the designation provided by the central pathology review.**
4. **An adequate tumor specimen obtained by either excisional biopsy, incisional biopsy or core needle biopsy must be sent to the central pathology lab for evaluation.**
5. Locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade with evidence of disease progression by either computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinical judgment on or after the last cancer therapy within 6 months prior to randomization.
6. Relapsed or refractory (lack of response) to ≥1 course of systemic therapy regimen(s), excluding adjuvant or neoadjuvant chemotherapy, and is incurable by either surgery or radiation.
7. Capable of providing informed consent and complying with trial procedures.
8. ECOG PS 0-2.
9. Life expectancy >12 weeks.
10. Measurable tumor lesions according to RECIST 1.1 criteria.[50]
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. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 11 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and agree to continue use for 6 months after the final dose of study treatment.
13. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
14. Accessibility to the site that optimizes the subject's ability to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Palliative surgery and/or radiation treatment within 30 days prior to date of randomization.
3. Exposure to any investigational agent within 30 days of date of randomization.
4. Exposure to any systemic chemotherapy within 30 days of date of randomization.
5. An inadequate tumor specimen as defined by the central pathologist.
6. Current evidence/diagnosis of alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma (unless transformed to fibrosarcoma), Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas.
7. Evidence of central nervous system (CNS) metastasis who have not received prior definitive therapy for their lesions.
8. History of other malignancies except cured basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma *in situ*, superficial bladder cancer or carcinoma *in situ* of the cervix unless documented free of cancer for ≥5 years.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

9. Laboratory values: Screening serum creatinine >1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, hemoglobin <9 g/dL.
10. Anion gap > 16 meq/L (Central Laboratory) or arterial blood pH < 7.30 (as determined by the Local Laboratory).
11. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) (Appendix D) guidelines.
12. 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 F).
13. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications.
14. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
15. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
16. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
17. Known history of HIV infection.
18. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals. The Medical Monitor should be contacted for any uncertainties.
19. Major surgery within 30 days prior to date of randomization.
20. Current or past substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
21. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:

Approximately 400 subjects with metastatic, locally advanced or unresectable soft tissue sarcomas who have either not responded to or have progressed after treatment with 1 or more systemic regimens of non-adjuvant chemotherapies will be randomized 1:1 (aldoxorubicin:investigator's choice) at approximately 120 study centers in the US, Europe, Canada, Latin America, and Australia. The randomization will be stratified according to their initial PS (ECOG 0-1 vs 2), whether they had either 1 prior systemic non-adjuvant chemotherapy regimens or >1 prior systemic non-adjuvant chemotherapy regimens and whether they had received prior doxorubicin chemotherapy. Subjects will also be stratified by their histopathological diagnosis as determined by the local site. The four stratification groups will be leiomyosarcomas, liposarcoma, synovial sarcoma, and all other sarcomas.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Test Product, Dose and Mode of Administration:

Aldoxorubicin: Lyophilized powder in vials that contain 200 mg of aldoxorubicin reconstituted by adding a solution of 50% ethanol: 50% sterile water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent). Aldoxorubicin infusion may exceed 30 minutes if deemed necessary by the investigative site but the total time from the completion of reconstitution of aldoxorubicin to completion of infusion must not be more than 2 hours.

Investigator's Choice: Up to three treatment regimens are to be chosen by the investigator from the list below prior to the initiation of the study site and the treatment chosen for each subject enrolled in the study must be entered into the case report form. Directions for dosage and reconstitution should follow institutional standard of care, package inserts (SPCs), or the suggestions below based on the US package inserts and the literature.

Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, Sterile Water for Injection, USP. The resulting solution contains 10 mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously. The reconstituted solution may be further diluted with 5% dextrose injection, or sodium chloride injection (250 to 500 mL), and administered as an IVI over 90±15 minutes.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Pazopanib (Votrient®) 200 mg tablets can be stored at room temperature between 20° and 25°C; excursions are permitted between 15° and 30°C. Tablets are taken 1 hour before or 2 hours after a meal and tablets are NOT to be crushed.

Gemcitabine 200 mg or 1 g lyophilized powder in a single use vial is reconstituted with 0.9% NaCl to a final concentration of ≤40 mg/mL and pH 2.7 to 3.3. The reconstituted solution may be further diluted with 0.9% NaCl and administered by IVI in <60 minutes. It is stable for up to 24 hours at controlled room temperature (20° to 25°C) and should not be refrigerated.

Docetaxel 80 mg/8 mL and 20 mg/2 mL is administered by IVI over approximately 60 minutes after dilution into a 250 to 500 mL infusion bag of either 0.9% NaCl or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. Docetaxel final dilution for infusion should be administered within 4 hours of preparation. It can be stored between 2° and 25°C.

Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose and may be administered over 5 to 30 minutes.

Ifosamide single-dose vials for constitution and administration by IVI each contain 1 gram or 3 grams of sterile ifosfamide, USP. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Sterile Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved) to the vial and shaking to dissolve. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose solution and may be administered over 2 to 4 hours.

See Section 5.2 for additional investigator's choice treatment concentrations and preparation instructions as per package inserts.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Criteria for Evaluation:

Efficacy:

The following efficacy variables will be evaluated as noted:

- PFS.
- OS.
- Objective tumor response (RECIST 1.1 criteria[50]).
- Disease control rate (objective tumor response + stable disease at 4 months).
- Subject Reported Outcome as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire.

Safety:

The following safety variables will be assessed over the duration 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.

Pharmacokinetics:

The following PK variables will be assessed for aldoxorubicin, doxorubicin, and doxorubicinol:

- Maximum drug concentration (C_{max}) in plasma.
- Area under the plasma drug-concentration-time profile (AUC).
- Clearance (CL).
- Volume of distribution (V_d).
- Half-life ($t_{½}$).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects will be evaluated for efficacy. All subjects who receive at least 1 dose of study medication will be evaluated for safety.

Efficacy:
The primary analysis of PFS will be carried out when approximately 191 PFS events have been observed by the blinded Central Imaging Research Organization (approximately 15 months following the completion of enrollment of 400 subjects). Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

An important secondary endpoint is overall survival (OS). The analysis of OS will be considered confirmatory only if the PFS analysis is statistically significant. As a result, the nominal level of significance for the OS analysis will be α=0.05. However, because an interim analysis of OS will be carried out at the time of the analysis of PFS, the levels of significance for the interim and final analyses of OS will be α=0.00305 and α=0.049, respectively.

The final analysis of OS will be completed when 320 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided log rank test at the α=0.049 level of significance. The same methodology will be used for the interim analysis, but at the α=0.00305 level of significance.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression. The percentage of subjects with complete or PRs, or stable disease will be evaluated and the disease control rate (CR, PR and SD at 4 months) will be compared using Pearson's chi-square test, or if 20% or more of the expected cell frequencies are <5, Fisher's exact test. Patient reported outcomes as assessed by the EORTC Quality of Life Questionnaire will be analyzed using analysis of covariance.

Sample Size Justification:
Power calculations and subject numbers were calculated based on the primary endpoint of PFS. Reviewing the literature for studies that have evaluated gemcitabine + docetaxel, pazopanib, ifosfamide and dacarbazine as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the investigator's choice group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 5.6 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 191 events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 15 month follow-up period after enrollment of the last subject, approximately 400 subjects will be needed to achieve the total of 191 events.

Safety:
The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Pharmacokinetics: All subjects who receive aldoxorubicin and provide at least one PK sample with concentrations above the limit of quantification will be included in the PK analysis. Sparse plasma aldoxorubicin, doxorubicin, and doxorubicinol concentration data will be analyzed, and aldoxorubicin, doxorubicin, and doxorubicinol PK parameters will be estimated based on a population PK analysis. PK parameters will be summarized using descriptive statistics. Exploratory exposure-response/exposure-safety analyses will be conducted using the primary and secondary efficacy endpoints, PFS and OS, and for selected AEs.	

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3[22]	Cycle 4[22]	Cycle 5[22]	Cycle 6[22]	Cycle 7[22]	Cycle 8[22], 9+[22]	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
GENERAL AND SAFETY														
Informed Consent	X													
Review Inclusion/Exclusion	X	X												
Tumor Specimen[1]	X													
Randomization[2]		X												
Medical History[3]	X													
Physical Examination[4]	X	X	X	X	X	X	X	X	X		X[25]	X[25]	X[25]	
Height (cm)	X	X[5]												
Weight (kg)	X	X	X	X	X	X	X	X	X					
BSA Calculation[5]		X	X	X	X	X	X	X	X					
Vital Signs[6]	X	X	X	X	X	X	X	X	X		X	X	X	
Adverse Events[7]		X	X	X	X	X	X	X	X		X			
Survival Follow-Up[8]														X
ECOG PS	X	X	X	X	X	X	X	X	X		X			
Concomitant Medications	X[9]	X	X	X	X	X	X	X	X		X			
RADIOGRAPHIC ASSESSMENTS														
CT/ MRI Scan / Tumor Measurements[10]	X[11a]			X[11]		X[11]		X[11]				X	X	
CARDIAC ASSESSMENTS														
ECG[12]	X	X	X	X	X	X	X	X	X		X[26]	X	X	
ECHO (with ejection fraction)[13]	X		X		X		X		X		X	X	X	
CENTRAL LAB ASSESSMENTS														
CBC w/differential & Platelets[14]	X	X[16]	X	X	X	X	X	X	X	X	X[26]	X	X	
Serum Chemistries[14, 15]	X	X[16]	X	X	X	X	X	X	X	X	X[26]			
Pharmacokinetic Sampling[18]		X												
Urinalysis[17]	X										X[26]			
Serum/Urine Pregnancy Test	X													

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3[22]	Cycle 4[22]	Cycle 5[22]	Cycle 6[22]	Cycle 7[22]	Cycle 8[22], 9+[22]	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
LOCAL LAB ASSESSMENTS[27]														
CBC w/differential & Platelets[14]	X*	X[16]	X	X	X	X	X	X	X	X				
Serum Chemistries [14, 15]		X[16]	X	X	X	X	X	X	X	X				
QUALITY OF LIFE QUESTIONNAIRE														
EORTC QLQ-C30 Version 3	X				X						X			
CHEMOTHERAPY: ALDOXORUBICIN OR INVESTIGATOR'S CHOICE														
Aldoxorubicin, Doxorubicin, Ifosfamide or Dacarbazine Administration[19]		X	X	X	X	X	X	X	X					
Gemcitabine and Docetaxel Administration [20]		X	X	X	X	X	X	X	X					
Pazopanib Administration and Diary[21]		X	X	X	X	X	X	X	X					

NOTE: All assessment must be performed within 72 hours of each specified time parameter (48 hours for pazopanib treated subjects), except Cycle 1 (see Section 6 for details).

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

CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy**

PROTOCOL NUMBER: **ALDOXORUBICIN-P3-STS-01**

STUDY DRUG: **Aldoxorubicin**

IND NUMBER: **113,695**

EUDRACT NUMBER: **2013-004103-40**

SPONSOR: **CytRx Corporation**
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ORIGINAL PROTOCOL: **April 3, 2013**
AMENDMENT 1: **August 28, 2013**
AMENDMENT 2: **March 21, 2014**
AMENDMENT 3: **January 13, 2015**
AMENDMENT 4: **April 13, 2015**
AMENDMENT 5: **January 21, 2016**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation (CytRx) prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partner] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CytRx.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: May 2, 2016

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator's Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator's choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS). **Secondary Objectives:** The secondary objectives of this study are to evaluate the efficacy of aldoxorubicin as measured by overall survival (OS), overall response rate (ORR), disease control rate (ORR + SD at 4 months), PFS at 4 and 6 months, safety of aldoxorubicin compared to investigator's choice 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. **Exploratory Objectives:** To determine the sparse pharmacokinetics (PK) of aldoxorubicin, doxorubicin, and doxorubicinol following intravenous (IV) administration of aldoxorubicin, and to evaluate the exposure-response relationships between aldoxorubicin, doxorubicin, and/or doxorubicinol and PFS, OS, selected safety parameters, and quality of life (EORTC QLQ-C30).	
Study Rationale and Significance: Aldoxorubicin (INNO-206; DOXO-EMCH) is a novel prodrug that binds covalently to circulating albumin. 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 antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas who have failed prior chemotherapies have a poor prognosis with PFS of around 2-4.6 months and median OS of approximately 9-12 months. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as ifosfamide, gemcitabine, docetaxel, vinorelbine, dacarbazine, temozolomide, epirubicin, pazopanib and liposomal doxorubicin. However, these regimens can be quite toxic and have not significantly impacted either progression-free or OS in these individuals. Pazopanib, recently approved in the US and Europe, does appear to extend PFS in soft tissue sarcoma patients (except liposarcomas) who have relapsed after receiving prior chemotherapy compared to no treatment, but does not increase OS. Aldoxorubicin may improve upon the activity of doxorubicin without an increase in toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Design and Methodology:

This is a phase 3 open-label study evaluating the efficacy and safety of aldoxorubicin administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs compared to investigator's choice of treatment among 5 different therapies. These therapies include (dosages should follow the institutional standard of care, package insert (SPCs), or the following suggestions based on the US package inserts and the literature): 1) dacarbazine administered at 1000 mg/m^2 by intravenous infusion (IVI), over 90±15 minutes on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs; 2) pazopanib, 800 mg orally each day until tumor progression or unacceptable toxicity occurs; 3) gemcitabine, 900 mg/m^2 by IVI in less than 60 minutes on Days 1 and 8, plus docetaxel, 100 mg/m^2 by IVI over 1 hour on Day 8 of a 21 day cycle until tumor progression or unacceptable toxicity occurs; 4) doxorubicin, 75 mg/m^2 by IVI over 5 to 30 minutes every 21 days for a maximum cumulative dose of 550 mg/m^2 or unacceptable toxicity occurs; or 5) ifosfamide 2.0 g/m^2 administered over 2 to 4 hours on Days 1-4 of a 21 day cycle + mesna per standard site administration regimen until tumor progression or unacceptable toxicity occurs. The investigative site must **pre-specify** their choice of treatments for the comparator arm to be used at their site, and no more than 3 treatment regimens may be selected for the comparator arm at each site which must be selected **prior** to the study site initiation visit. Subjects will be randomized 1:1 to receive either aldoxorubicin or investigator's choice of up to 3 control regimens pre-selected by the study site. Treatment with G-CSF should be administered to all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E). **Note: aldoxorubicin has been associated with >20% incidence of grade 3 or 4 neutropenia. Therefore, the administration of G-CSF should occur even during Cycle 1.**

All Screening requirements, including an ECHO exam, must be completed within 28 days of the Cycle 1-Day 1 visit. Subjects receiving aldoxorubicin, ifosfamide, dacarbazine or doxorubicin will visit the study site on Day 1 of each cycle. They will have complete blood counts (CBC) and serum chemistries on Day 15 and Day 21 (if Day 21 does not correspond to Day 1 of the next cycle, ±3 days) of each cycle as well. Subjects receiving pazopanib will visit the study site on Day 1 of their next cycle for monitoring, testing (same as for Day 1 for other treatment regimens) and to receive a new supply of study drug. Subjects receiving pazopanib will also have CBC and serum chemistry on Day 15 and Day 28 (if Day 28 does not correspond to Day 1 of the next cycle, ±2 days). Subjects receiving gemcitabine plus docetaxel will visit the study site on both days of their infusions (Days 1 and 8) and at Days 15 and 21 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, CBC, and urinalysis), vital signs, weight measurements, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and ECGs will be performed on Day 1 (for all subjects) of each cycle. Subjects receiving aldoxorubicin will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically (per Schedule of Treatment and Evaluations in Appendix A) with ECHOs for subjects receiving either aldoxorubicin or doxorubicin. Treatment will continue until tumor progression is observed, a maximum cumulative dose of 550 mg/m^2 is reached (doxorubicin), subject asks to withdraw, unacceptable toxicity occurs, a change in therapy would be in the best interest of the subject, subject becomes pregnant or fails to use adequate birth control, need for any treatment not allowed by the protocol, or subject is non-compliant with study requirements.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[50] OS, PFS, and PFS at 4 and 6 months will be evaluated. Objective overall response rate (ORR) (complete and partial responses [PRs]), disease control rate (objective responses plus stable disease at 4 months) and quality of life will be assessed.

The PK of aldoxorubicin, doxorubicin, and doxorubicinol will be evaluated using a sparse sample analysis. Plasma samples will be collected from subjects receiving aldoxorubicin at Cycle 1 at the following time points: the end of the infusion, between 1.5 and 4 hours from the end of the infusion, and on Days 2, and 3. If necessary and possible, PK samples may be collected at a later cycle along with collecting a predose blood sample.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Has provided written informed consent prior to any study related activities.
2. Age ≥15 years (US only), and 18-80 (rest of world (ROW)), male or female.
3. Histological confirmation of intermediate or high grade soft-tissue sarcoma as determined by the local pathology report. Archival tissue must be sent to a central pathology lab for review but will not preclude entry onto the study (study-specific biopsies are not allowed). **Final assignment of tumor grade and histology will be based on the designation provided by the central pathology review.**
4. **An adequate tumor specimen obtained by either excisional biopsy, incisional biopsy or core needle biopsy must be sent to the central pathology lab for evaluation.**
5. Locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade with evidence of disease progression by either computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinical judgment on or after the last cancer therapy within 6 months prior to randomization.
6. Relapsed or refractory (lack of response) to ≥1 course of systemic therapy regimen(s), excluding adjuvant or neoadjuvant chemotherapy, and is incurable by either surgery or radiation.
7. Capable of providing informed consent and complying with trial procedures.
8. ECOG PS 0-2.
9. Life expectancy >12 weeks.
10. Measurable tumor lesions according to RECIST 1.1 criteria.[50]
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. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 11 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and agree to continue use for 6 months after the final dose of study treatment.
13. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
14. Accessibility to the site that optimizes the subject's ability to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Palliative surgery and/or radiation treatment within 30 days prior to date of randomization.
3. Exposure to any investigational agent within 30 days of date of randomization.
4. Exposure to any systemic chemotherapy within 30 days of date of randomization.
5. An inadequate tumor specimen as defined by the central pathologist.
6. Current evidence/diagnosis of alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma (unless transformed to fibrosarcoma), Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas.
7. Evidence of central nervous system (CNS) metastasis who have not received prior definitive therapy for their lesions.
8. History of other malignancies except cured basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma *in situ*, superficial bladder cancer or carcinoma *in situ* of the cervix unless documented free of cancer for ≥5 years.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

9. Laboratory values: Screening serum creatinine >1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, absolute neutrophil count (ANC) <1,500/mm^3, platelet concentration <100,000/mm^3, hemoglobin <9 g/dL.
10. Anion gap > 16 meq/L (Central Laboratory) or arterial blood pH < 7.30 (as determined by the Local Laboratory).
11. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) (Appendix D) guidelines.
12. 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 F).
13. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications.
14. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
15. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
16. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
17. Known history of HIV infection.
18. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals. The Medical Monitor should be contacted for any uncertainties.
19. Major surgery within 30 days prior to date of randomization.
20. Current or past substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
21. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:

Approximately 400 subjects with metastatic, locally advanced or unresectable soft tissue sarcomas who have either not responded to or have progressed after treatment with 1 or more systemic regimens of non-adjuvant chemotherapies will be randomized 1:1 (aldoxorubicin:investigator's choice) at approximately 79 study centers in the US, Europe, Canada, Latin America, and Australia. The randomization will be stratified according to their initial PS (ECOG 0-1 vs 2), whether they had either 1 prior systemic non-adjuvant chemotherapy regimens or >1 prior systemic non-adjuvant chemotherapy regimens and whether they had received prior doxorubicin chemotherapy. Subjects will also be stratified by their histopathological diagnosis as determined by the local site. The four stratification groups will be leiomyosarcomas, liposarcoma, synovial sarcoma, and all other sarcomas.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Test Product, Dose and Mode of Administration:

Aldoxorubicin: Lyophilized powder in vials that contain 200 mg of aldoxorubicin reconstituted by adding a solution of 50% ethanol: 50% sterile water, administration completed within 2 hours (of being reconstituted) as a 30-minute IVI Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent). Aldoxorubicin infusion may exceed 30 minutes if deemed necessary by the investigative site but the total time from the completion of reconstitution of aldoxorubicin to completion of infusion must not be more than 2 hours.

Investigator's Choice: Up to three treatment regimens are to be chosen by the investigator from the list below prior to the initiation of the study site and the treatment chosen for each subject enrolled in the study must be entered into the case report form. Directions for dosage and reconstitution should follow institutional standard of care, package inserts (SPCs), or the suggestions below based on the US package inserts and the literature.

Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, Sterile Water for Injection, USP. The resulting solution contains 10 mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously. The reconstituted solution may be further diluted with 5% dextrose injection, or sodium chloride injection (250 to 500 mL), and administered as an IVI over 90±15 minutes.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Pazopanib (Votrient®) 200 mg tablets can be stored at room temperature between 20° and 25°C; excursions are permitted between 15° and 30°C. Tablets are taken 1 hour before or 2 hours after a meal and tablets are NOT to be crushed.

Gemcitabine 200 mg or 1 g lyophilized powder in a single use vial is reconstituted with 0.9% NaCl to a final concentration of ≤40 mg/mL and pH 2.7 to 3.3. The reconstituted solution may be further diluted with 0.9% NaCl and administered by IVI in <60 minutes. It is stable for up to 24 hours at controlled room temperature (20° to 25°C) and should not be refrigerated.

Docetaxel 80 mg/8 mL and 20 mg/2 mL is administered by IVI over approximately 60 minutes after dilution into a 250 to 500 mL infusion bag of either 0.9% NaCl or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. Docetaxel final dilution for infusion should be administered within 4 hours of preparation. It can be stored between 2° and 25°C.

Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose and may be administered over 5 to 30 minutes.

Ifosamide single-dose vials for constitution and administration by IVI each contain 1 gram or 3 grams of sterile ifosfamide, USP. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Sterile Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved) to the vial and shaking to dissolve. The reconstituted solution is diluted in 0.9% NaCl or 5% dextrose solution and may be administered over 2 to 4 hours.

See Section 5.2 for additional investigator's choice treatment concentrations and preparation instructions as per package inserts.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Criteria for Evaluation:

Efficacy:

The following efficacy variables will be evaluated as noted:

- PFS.
- OS.
- Objective tumor response (RECIST 1.1 criteria[50]).
- Disease control rate (objective tumor response + stable disease at 4 months).
- PFS at 4 and 6 months.
- Subject Reported Outcome as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire.

Safety:

The following safety variables will be assessed over the duration 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.

Pharmacokinetics:

The following PK variables will be assessed for aldoxorubicin, doxorubicin, and doxorubicinol:

- Maximum drug concentration (C_{max}) in plasma.
- Area under the plasma drug-concentration-time profile ($AUC_{0\text{-}inf}$).
- Clearance (CL).
- Volume of distribution (V_d).
- Half-life ($t_{½}$).

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3

Statistical Methods:
In accordance with the intention-to-treat principle, all randomized subjects will be evaluated for efficacy. All subjects who receive at least 1 dose of study medication will be evaluated for safety.

Efficacy:
The primary analysis of PFS will be carried out when approximately 191 PFS events have been observed by the blinded Central Imaging Research Organization (approximately 15 months following the completion of enrollment of 400 subjects). Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided unstratified log rank test at the $\alpha=0.05$ level of significance.

An important secondary endpoint is overall survival (OS). The analysis of OS will be considered confirmatory only if the PFS analysis is statistically significant. As a result, the nominal level of significance for the OS analysis will be $\alpha=0.05$. However, because an interim analysis of OS will be carried out at the time of the analysis of PFS, the levels of significance for the interim and final analyses of OS will be $\alpha=0.00305$ and $\alpha=0.049$, respectively.

The final analysis of OS will be completed when 320 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the two groups will be compared using a two-sided unstratified log rank test at the $\alpha=0.049$ level of significance. The same methodology will be used for the interim analysis, but at the $\alpha=0.00305$ level of significance.

Tumor response will be monitored at screening, every 6 weeks from Cycle 1-Day 1 through Week 30, and then every 12 weeks until disease progression. The percentage of subjects with complete or PRs, or stable disease will be evaluated and the disease control rate (CR, PR and SD at 4 months) will be compared using Pearson's chi-square test, or if 20% or more of the expected cell frequencies are <5, Fisher's exact test. Patient reported outcomes as assessed by the EORTC Quality of Life Questionnaire will be analyzed using analysis of covariance.

Sample Size Justification:
Power calculations and subject numbers were calculated based on the primary endpoint of PFS. Reviewing the literature for studies that have evaluated gemcitabine + docetaxel, pazopanib, ifosfamide and dacarbazine as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the investigator's choice group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 5.6 months. Based on the use of a two-sided log rank test at the $\alpha=0.05$ level of significance, a total of 191 events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 15 month follow-up period after enrollment of the last subject, approximately 400 subjects will be needed to achieve the total of 191 events.

Safety:
The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. AEs, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P3-STS-01	**Phase of Development:** 3
Pharmacokinetics: All subjects who receive aldoxorubicin and provide at least one PK sample with concentrations above the limit of quantification will be included in the PK analysis. Sparse plasma aldoxorubicin, doxorubicin, and doxorubicinol concentration data will be analyzed, and aldoxorubicin, doxorubicin, and doxorubicinol PK parameters will be estimated based on a population PK analysis. PK parameters will be summarized using descriptive statistics. Exploratory exposure-response/exposure-safety analyses will be conducted using the primary and secondary efficacy endpoints, PFS and OS, and for selected AEs.	

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3[22]	Cycle 4[22]	Cycle 5[22]	Cycle 6[22]	Cycle 7[22]	Cycle 8[22], 9+[22]	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
GENERAL AND SAFETY														
Informed Consent	X													
Review Inclusion/Exclusion	X	X												
Tumor Specimen[1]	X													
Randomization[2]		X												
Medical History[3]	X													
Physical Examination[4]	X	X	X	X	X	X	X	X	X		X[25]	X[25]	X[25]	
Height (cm)	X	X[5]												
Weight (kg)	X	X	X	X	X	X	X	X	X					
BSA Calculation[5]		X	X	X	X	X	X	X	X					
Vital Signs[6]	X	X	X	X	X	X	X	X	X		X	X	X	
Adverse Events[7]		X	X	X	X	X	X	X	X		X			
Survival Follow-Up[8]														X
ECOG PS	X	X	X	X	X	X	X	X	X		X			
Concomitant Medications	X[9]	X	X	X	X	X	X	X	X		X			
RADIOGRAPHIC ASSESSMENTS														
CT/ MRI Scan / Tumor Measurements[10]	X[11a]			X[11]		X[11]		X[11]				X	X	
CARDIAC ASSESSMENTS														
ECG[12]	X	X	X	X	X	X	X	X	X		X[26]	X	X	
ECHO (with ejection fraction)[13]	X		X		X		X		X		X	X	X	
CENTRAL LAB ASSESSMENTS														
CBC w/differential & Platelets[14]	X	X[16]	X	X	X	X	X	X	X	X	X[26]	X	X	
Serum Chemistries[14, 15]	X	X[16]	X	X	X	X	X	X	X	X	X[26]			
Pharmacokinetic Sampling[18]		X												
Urinalysis[17]	X										X[26]			
Serum/Urine Pregnancy Test	X													

	Screening -28 Days	Cycle 1	Cycle 2[22]	Cycle 3[22]	Cycle 4[22]	Cycle 5[22]	Cycle 6[22]	Cycle 7[22]	Cycle 8[22], 9+[22]	Day 15 and 21 (28 for pazopanib) each Cycle	End of Treatment[23]	Every 6 Weeks → Week 30[24]	Every 12 Weeks[24]	Follow Up
LOCAL LAB ASSESSMENTS[27]														
CBC w/differential & Platelets[14]	X*	X[16]	X	X	X	X	X	X	X	X				
Serum Chemistries [14, 15]		X[16]	X	X	X	X	X	X	X	X				
QUALITY OF LIFE QUESTIONNAIRE														
EORTC QLQ-C30 Version 3	X				X						X			
CHEMOTHERAPY: ALDOXORUBICIN OR INVESTIGATOR'S CHOICE														
Aldoxorubicin, Doxorubicin, Ifosfamide or Dacarbazine Administration[19]		X	X	X	X	X	X	X	X					
Gemcitabine and Docetaxel Administration [20]		X	X	X	X	X	X	X	X					
Pazopanib Administration and Diary[21]		X	X	X	X	X	X	X	X					

NOTE: All assessment must be performed within 72 hours of each specified time parameter (48 hours for pazopanib treated subjects), except Cycle 1 (see Section 6 for details).

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