CLINICAL PROTOCOL

TITLE:	**An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P1/2-STS-03**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**113,695**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd., Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-800-772-2215**
SAFETY FAX:	**1-888-772-6919**
SAFETY EMAIL:	**CHOsafety@praintl.com**
DATE OF PROTOCOL:	**June 30, 2014**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2
Title of the Protocol: An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary safety of administration of aldoxorubicin in combination with ifosfamide in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiograms (ECHO) or multiple-gated acquisition (MUGA) scans, electrocardiogram (ECG) results, and weight. **Secondary Objectives:** The secondary objective of this study is to evaluate the activity of aldoxorubicin in combination with ifosfamide/mesna in this population, assessed by overall response rate, progression-free survival (PFS) and PFS at 4 and 6 months.	
Study Rationale and Significance: Aldoxorubicin is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models and in patients with soft tissue sarcomas when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months after treatment with single agent doxorubicin. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, as currently administered these regimens are quite toxic and have not significantly increased survival in these individuals. Aldoxorubicin in combination with a less toxic schedule for administering ifosfamide may improve the activity of this combination without increasing its toxicity as has been demonstrated for ifosfamide as a single agent.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Design and Methodology:

This is a phase 1b/2 open-label study evaluating the preliminary safety and activity of aldoxorubicin administered at either 170, 250 or 350 mg/m^2 (125, 185 and 260 mg/m^2 doxorubicin equivalents) intravenously (IV) on Day 1 every 28 days plus 1 gm/m^2/day **ifosfamide by continuous intravenous infusion for up to 14 days via a portable/ambulatory infusion pump using a central line such as port-a-cath or PICC line every** 28 days starting on Day 1 of each cycle, with equivalent dose of mesna via IV infusion daily with ifosfamide administration until disease progression, unacceptable toxicity or withdrawal of consent. A subsequent dose level of aldoxorubicin may be administered if < 2 of 3 or < 3 of 6 subjects experience a DLT during Cycles 1 and 2. The subsequent dose level may not be initiated until all subjects have completed at least 2 cycles at the current dose level and approval is granted by the CytRx Medical Monitor.

Subjects will visit the study site every 28 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, ECOG performance status and ECGs will be performed. Cardiac function will also be followed periodically using either ECHO or MUGA scans. All subjects will have a CBC on Days 8, 11, 15, and 21 and a basic metabolic panel on Days 8, 15, and 21 at either the study site or at their local laboratory. Treatment will continue every 28 days until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Subjects will return to the study site on Days 4, 8, and 11 to have their ifosfamide infusion pump re-filled and receive intravenous anti-emetics and hydration therapy, if necessary. On Day 15, subjects will return to the study site to have their infusion pump turned off.

Tumor response will be monitored every 8 weeks from Cycle 1-Day 1 through week 33, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. For those subjects who stop treatment for reasons other than disease progression and who do not start another therapy, will be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. Progression-free survival, progression-free survival at 4 and 6 months will be monitored as other primary objectives.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age between 15-80 years, male or female.
2. Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma (including rhabdomyosarcoma, Ewing's sarcoma and mixed mesodermal sarcoma), chondrosarcoma or osteosarcoma of intermediate or high grade and gastrointestinal stromal tumors (GIST) (only in subjects that have progressed after receiving treatment with imatinib and sunitinib).
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-2.
6. Life expectancy >12 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.
8. Women must not be able to become pregnant (eg 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.)
9. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 8 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and for 6 months after the final dose of study treatment.
10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
3. Palliative surgery and/or radiation treatment less than 30 days prior to enrollment.
4. Exposure to any investigational agent within 30 days of enrollment.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, dermatofibrosarcoma, Kaposi's sarcoma, clear cell sarcomas and unresectable low grade liposarcomas.
7. Central nervous system metastasis if symptomatic.
8. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for ≥ 5 years.
9. Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, albumin <2 gm/dL, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN.
10. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

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.
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed
13. History or signs of active coronary artery disease with or without angina pectoris.
14. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
15. History of HIV infection.
16. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
17. Major surgery within 21 days prior to enrollment.
18. Substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
19. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 30 study subjects will be treated at US study centers.

Test Product, Dose and Mode of Administration:
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 IV infusion in Lactated Ringer's solution. Total dose of 170, 250 or 350 mg/m^2 (125, 185 or 260 mg/m^2 doxorubicin equivalents).

Ifosfamide 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 as a continuous IV infusion for 14 consecutive days.

Adjunctive Therapy, Dose and Mode of Administration:
Mesna Injection is a sterile, nonpyrogenic, aqueous solution of colorless to light pink appearance in clear glass multidose vials for intravenous administration. Mesna injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium, sodium hydroxide for pH adjustment and q.s with Water for Injection. Mesna injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. The solution has a pH range of 6.5 to 7.4.

Criteria for Evaluation:

Activity:
The following activity variables will be evaluated as noted:

- Progression-free survival
- Objective tumor response (RECIST 1.1 criteria)
- 4 and 6 month progression-free survival

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Safety:

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

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

Statistical Methods:

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

Activity:

Tumor response will be monitored every 8 weeks from Cycle 1-Day1 through week 33, and then every 12 weeks until disease progression. For the estimation of progression-free a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 4 and 6 months.

Safety:

The safety data will be summarized by treatment group. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be summarized for each cohort. Adverse events, 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 groups. 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.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Day 1 of each Cycle	Day 4 of each Cycle	Day 8 of each Cycle	Day 11 of each Cycle	Day 15 of each Cycle	Day 21 of each Cycle	At end of every even Cycle	Every 8 weeks from Day 1 Cycle 1	End of Treatment[13]	Every 2 or 3 mo.[12]
Signed informed consent	X										
Review inclusion/exclusion		X									
Medical history[1]	X										
Physical examination	X	X								X	X
Height (cm)	X										
Weight (kg)	X	X									
BSA calculation[2]		X									
Vital signs[3]	X	X								X	X
ECOG PS	X	X								X	
CT/ MRI scan / tumor measurements[4]	X[8a]								X[8]	X[10]	X
ECG	X	X								X[11]	X
ECHO (with ejection fraction) or MUGA	X							X[17]		X	X
CBC w/differential & plts[5]	X	X		X	X	X	X			X[11]	X
Coagulation tests (PT, PTT, INR)	X										
Serum chemistries [5, 6, 14]	X	X		X[18]		X[18]	X[18]			X[11]	
Urinalysis[7]	X									X[11]	
Serum/urine pregnancy test	X										
Aldoxorubicin and ifosfamide/mesna administration[15]		X									
Re-fill infusion pump, provide IV anti-emetics and hydration therapy, if necessary			X	X	X						
Stop infusion pump						X					
Filgrastim or pegfilgrastim administration[16]						X					
Concomitant medications	X[9]	X								X	
Adverse events		X								X	

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

CLINICAL PROTOCOL

TITLE:	**An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P1/2-STS-03**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**113,695**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd., Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-800-772-2215**
SAFETY FAX:	**1-888-772-6919**
SAFETY EMAIL:	**CHOsafety@praintl.com**
DATE OF PROTOCOL:	**June 30, 2014**
AMENDMENT 1:	**January 13, 2015**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2
Title of the Protocol: An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary safety of administration of aldoxorubicin in combination with ifosfamide in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiograms (ECHO) or multiple-gated acquisition (MUGA) scans, electrocardiogram (ECG) results, and weight. **Secondary Objectives:** The secondary objective of this study is to evaluate the activity of aldoxorubicin in combination with ifosfamide/mesna in this population, assessed by overall response rate, progression-free survival (PFS) and PFS at 4 and 6 months.	
Study Rationale and Significance: Aldoxorubicin is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models and in patients with soft tissue sarcomas when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months after treatment with single agent doxorubicin. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, as currently administered these regimens are quite toxic and have not significantly increased survival in these individuals. Aldoxorubicin in combination with a less toxic schedule for administering ifosfamide may improve the activity of this combination without increasing its toxicity as has been demonstrated for ifosfamide as a single agent.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Design and Methodology:

This is a phase 1b/2 open-label study evaluating the preliminary safety and activity of aldoxorubicin administered at either 170, 250 or 350 mg/m^2 (125, 185 and 260 mg/m^2 doxorubicin equivalents) intravenously (IV) on Day 1 every 28 days plus 1 gm/m^2/day **ifosfamide by continuous intravenous infusion for up to 14 days via a portable/ambulatory infusion pump using a central line such as port-a-cath or PICC line every** 28 days starting on Day 1 of each cycle, with equivalent dose of mesna via IV infusion daily with ifosfamide administration until disease progression, unacceptable toxicity or withdrawal of consent. A subsequent dose level of aldoxorubicin may be administered if < 2 of 3 or < 3 of 6 subjects experience a DLT during Cycles 1 and 2. The subsequent dose level may not be initiated until all subjects have completed at least 2 cycles at the current dose level and approval is granted by the CytRx Medical Monitor. Treatment with granulocyte colony-stimulating factor (G-CSF) should be administered for all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E). **Note: aldoxorubicin, at higher doses, has been associated with >20% incidence of grade 3 or 4 neutropenia.**

Subjects will visit the study site every 28 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry and complete blood count [CBC]), vital signs, weight measurements, ECOG performance status and ECGs will be performed. All subjects will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically using either ECHO or MUGA scans. All subjects will have a CBC on Days 8, 11, 15, and 21 and a basic metabolic panel on Days 8, 15, and 21 at either the study site or at their local laboratory. Treatment will continue every 28 days until tumor progression is observed, unacceptable toxicity occurs, or consent is withdrawn. Subjects will return to the study site on Days 4, 8, and 11 to have their ifosfamide infusion pump re-filled and receive intravenous anti-emetics and hydration therapy, if necessary. On Day 15, subjects will return to the study site to have their infusion pump turned off.

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day 1 through week 32, and then every 12 weeks (±5 days) until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. For those subjects who stop treatment for reasons other than disease progression and who do not start another therapy, will be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. Progression-free survival, progression-free survival at 4 and 6 months will be monitored as other primary objectives.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age between 15-80 years, male or female.
2. Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma (including rhabdomyosarcoma, Ewing's sarcoma and mixed mesodermal sarcoma), chondrosarcoma or osteosarcoma of intermediate or high grade and gastrointestinal stromal tumors (GIST) (only in subjects that have progressed after receiving treatment with imatinib and sunitinib).
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-2.
6. Life expectancy >12 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.
8. Women must not be able to become pregnant (eg 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.)
9. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 8 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and for 6 months after the final dose of study treatment.
10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
3. Palliative surgery and/or radiation treatment less than 30 days prior to enrollment.
4. Exposure to any investigational agent within 30 days of enrollment.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, dermatofibrosarcoma, Kaposi's sarcoma, clear cell sarcomas and unresectable low grade liposarcomas.
7. Anion gap > 16 meq/L or arterial blood pH < 7.30.
8. Central nervous system metastasis if symptomatic.
9. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for ≥ 5 years.

   Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, albumin <2 gm/dL, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

11. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) 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.
13. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed
14. History or signs of active coronary artery disease with or without angina pectoris.
15. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
16. History of HIV infection.
17. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
18. Major surgery within 21 days prior to enrollment.
19. 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:
Up to 30 study subjects will be treated at US study centers.

Test Product, Dose and Mode of Administration:
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 IV infusion in Lactated Ringer's solution. Total dose of 170, 250 or 350 mg/m^2 (125, 185 or 260 mg/m^2 doxorubicin equivalents).

Ifosfamide 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 as a continuous IV infusion for 14 consecutive days.

Adjunctive Therapy, Dose and Mode of Administration:
Mesna Injection is a sterile, nonpyrogenic, aqueous solution of colorless to light pink appearance in clear glass multidose vials for intravenous administration. Mesna injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium, sodium hydroxide for pH adjustment and q.s with Water for Injection. Mesna injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. The solution has a pH range of 6.5 to 7.4.

Criteria for Evaluation:

Activity:
The following activity variables will be evaluated as noted:

- Progression-free survival
- Objective tumor response (RECIST 1.1 criteria)
- 4 and 6 month progression-free survival

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Safety:

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

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

Statistical Methods:

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

Activity:

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day1 through week 32, and then every 12 weeks (±5 days) until disease progression. For the estimation of progression-free a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 4 and 6 months.

Safety:

The safety data will be summarized by treatment group. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be summarized for each cohort. Adverse events, 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 groups. 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.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Day 1 of each Cycle	Day 4 of each Cycle**	Day 8 of each Cycle	Day 11 of each Cycle**	Day 15 of each Cycle	Day 21 of each Cycle	At end of every even Cycle	Every 8 weeks from Day 1 Cycle 1	End of Treatment[13]	Every 2 or 3 mo.[12]
Signed informed consent	X										
Review inclusion/exclusion		X									
Medical history[1]	X										
Physical examination	X	X								X	X
Height (cm)	X										
Weight (kg)	X	X									
BSA calculation[2]		X									
Vital signs[3]	X	X								X	X
ECOG PS	X	X								X	
CT/ MRI scan / tumor measurements[4]	X[8a]								X[8]	X[10]	X
ECG	X	X								X[11]	X
ECHO (with ejection fraction) or MUGA	X							X[17]		X	X
CBC w/differential & plts[5]	X	X		X	X	X	X			X[11]	X
Coagulation tests (PT, PTT, INR)	X										
Serum chemistries [5, 6, 14]	X*	X		X[18]		X[18]	X[18]			X[11]	
Urinalysis[7]	X									X[11]	
Serum/urine pregnancy test	X										
Aldoxorubicin and ifosfamide/mesna administration[15]		X									
Re-fill infusion pump, provide IV anti-emetics and hydration therapy, if necessary			X	X	X						
Stop infusion pump						X					
Filgrastim or pegfilgrastim administration[16]						X					
Concomitant medications	X[9]	X								X	
Adverse events		X								X	

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1 (see Section 6 for details).
*Arterial blood gas test may be done, if needed, to confirm acid levels. **±2 days

CLINICAL PROTOCOL

TITLE:	**An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P1/2-STS-03**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**113,695**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd., Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-800-772-2215**
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SAFETY EMAIL:	**CHOsafety@praintl.com**
DATE OF PROTOCOL:	**June 30, 2014**
AMENDMENT 1:	**January 13, 2015**
AMENDMENT 2:	**September 1, 2015**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2
Title of the Protocol: An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary safety of administration of aldoxorubicin in combination with ifosfamide in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiograms (ECHO) or multiple-gated acquisition (MUGA) scans, electrocardiogram (ECG) results, and weight. **Secondary Objectives:** The secondary objective of this study is to evaluate the activity of aldoxorubicin in combination with ifosfamide/mesna in this population, assessed by overall response rate, progression-free survival (PFS) and PFS at 4 and 6 months.	
Study Rationale and Significance: Aldoxorubicin is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models and in patients with soft tissue sarcomas when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months after treatment with single agent doxorubicin. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, as currently administered these regimens are quite toxic and have not significantly increased survival in these individuals. Aldoxorubicin in combination with a less toxic schedule for administering ifosfamide may improve the activity of this combination without increasing its toxicity as has been demonstrated for ifosfamide as a single agent.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Design and Methodology:

This is a phase 1b/2 open-label study evaluating the preliminary safety and activity of aldoxorubicin administered at either 170 or 250 mg/m^2 (125 and 185 mg/m^2 doxorubicin equivalents) intravenously (IV) on Day 1 every 28 days plus 1 gm/m^2/day **ifosfamide by continuous intravenous infusion for up to 10-14 days (based on tolerability) via a portable/ambulatory infusion pump using a central line such as port-a-cath or PICC line every** 28 days starting on Day 1 of each cycle, with equivalent dose of mesna via IV infusion daily with ifosfamide administration for 6 cycles. A subsequent dose level of aldoxorubicin may be administered if < 2 of 3 or < 3 of 6 subjects experience a DLT during Cycles 1 and 2. The subsequent dose level may not be initiated until all subjects have completed at least 2 cycles at the current dose level and approval is granted by the CytRx Medical Monitor. Treatment with granulocyte colony-stimulating factor (G-CSF) should be administered for all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E). **Note: aldoxorubicin, at higher doses, has been associated with >20% incidence of grade 3 or 4 neutropenia.** Subjects with response (CR, PR, or SD) to initial combination therapy may continue with aldoxorubicin alone every 21 days at the same dose as used with the combination until disease progression, unacceptable toxicity or withdrawal of consent.

Subjects will visit the study site every 28 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry and complete blood count [CBC]), vital signs, weight measurements, ECOG performance status and ECGs will be performed. All subjects will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically using either ECHO or MUGA scans. All subjects will have a CBC on Days 8, 11, 15, and 21 and a basic metabolic panel on Days 8, 15, and 21 at either the study site or at their local laboratory. Subjects will return to the study site on Days 4, 8, and 11 to have their ifosfamide infusion pump re-filled and receive intravenous anti-emetics and hydration therapy, if necessary. Between days 11-15, subjects will return to the study site to have their infusion pump turned off. Treatment with aldoxorubicin and ifosfamide/mesna will continue every 28 days for 6 cycles. Subjects with response (CR, PR, or SD) to initial combination therapy may continue with aldoxorubicin alone every 21 days at the same dose as used with the combination until disease progression is observed, unacceptable toxicity occurs, or consent is withdrawn.

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day 1 through week 32, and then every 12 weeks (±5 days) until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. For those subjects who stop treatment for reasons other than disease progression and who do not start another therapy, will be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. Progression-free survival, progression-free survival at 4 and 6 months will be monitored as other primary objectives.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age between 15-80 years, male or female.
2. Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma (including rhabdomyosarcoma, Ewing's sarcoma and mixed mesodermal sarcoma), chondrosarcoma or osteosarcoma of intermediate or high grade and gastrointestinal stromal tumors (GIST) (only in subjects that have progressed after receiving treatment with imatinib and sunitinib).
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-2.
6. Life expectancy >12 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.
8. Women must not be able to become pregnant (eg 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.)
9. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 8 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and for 6 months after the final dose of study treatment.
10. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
11. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
3. Palliative surgery and/or radiation treatment less than 30 days prior to enrollment.
4. Exposure to any investigational agent within 30 days of enrollment.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, dermatofibrosarcoma, Kaposi's sarcoma, clear cell sarcomas and unresectable low grade liposarcomas.
7. Anion gap > 16 meq/L or arterial blood pH < 7.30.
8. Central nervous system metastasis if symptomatic.
9. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for ≥ 5 years.
10. Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, albumin <2 gm/dL, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

11. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) 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.
13. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed
14. History or signs of active coronary artery disease with or without angina pectoris.
15. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
16. History of HIV infection.
17. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
18. Major surgery within 21 days prior to enrollment.
19. 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:
Up to 30 study subjects will be treated at US study centers.

Test Product, Dose and Mode of Administration:
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 IV infusion in Lactated Ringer's solution. Total dose of 170 or 250 mg/m^2 (125 and 185 mg/m^2 doxorubicin equivalents).

Ifosfamide 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 as a continuous IV infusion for 14 consecutive days.

Adjunctive Therapy, Dose and Mode of Administration:
Mesna Injection is a sterile, nonpyrogenic, aqueous solution of colorless to light pink appearance in clear glass multidose vials for intravenous administration. Mesna injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium, sodium hydroxide for pH adjustment and q.s with Water for Injection. Mesna injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. The solution has a pH range of 6.5 to 7.4.

Criteria for Evaluation:

Activity:
The following activity variables will be evaluated as noted:

- Progression-free survival
- Objective tumor response (RECIST 1.1 criteria)
- 4 and 6 month progression-free survival

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Safety:

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

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

Statistical Methods:

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

Activity:

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day1 through week 32, and then every 12 weeks (±5 days) until disease progression. For the estimation of progression-free a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 4 and 6 months.

Safety:

The safety data will be summarized by treatment group. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be summarized for each cohort. Adverse events, 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 groups. 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.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Day 1 of each Cycle	Day 4 of each Cycle**	Day 8 of each Cycle	Day 11 of each Cycle**	Day 11-15 of each Cycle	Day 21 of each Cycle	At end of every even Cycle	Every 8 weeks from Day 1 Cycle 1	End of Treatment[13]	Every 2 or 3 mo.[12]
Signed informed consent	X										
Review inclusion/exclusion		X									
Medical history[1]	X										
Physical examination	X	X								X	X
Height (cm)	X										
Weight (kg)	X	X									
BSA calculation[2]		X									
Vital signs[3]	X	X								X	X
ECOG PS	X	X								X	
CT/ MRI scan / tumor measurements[4]	X[8a]								X[8]	X[10]	X
ECG	X	X								X	X
ECHO (with ejection fraction) or MUGA	X							X[17]		X	X
CBC w/differential & plts[5]	X	X		X	X	X	X			X[11]	X
Coagulation tests (PT, PTT, INR)	X										
Serum chemistries [5, 6, 14]	X*	X		X[18]		X[18]	X[18]			X[11]	
Urinalysis[7]	X									X[11]	
Serum/urine pregnancy test	X										
Aldoxorubicin and ifosfamide/mesna administration[15]		X									
Re-fill infusion pump, provide IV anti-emetics and hydration therapy, if necessary			X	X	X						
Stop infusion pump						X					
Filgrastim or pegfilgrastim administration[16]						X					
Concomitant medications	X[9]	X								X	
Adverse events		X								X	

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1 (see Section 6 for details).
*Arterial blood gas test may be done, if needed, to confirm acid levels. **±2 days

CLINICAL PROTOCOL

TITLE:	**An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P1/2-STS-03**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**113,695**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd., Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-800-772-2215**
SAFETY FAX:	**1-888-772-6919**
SAFETY EMAIL:	**CHOsafety@praintl.com**
DATE OF PROTOCOL:	**June 30, 2014**
AMENDMENT 1:	**January 13, 2015**
AMENDMENT 2:	**September 1, 2015**
AMENDMENT 3:	**April 4, 2016**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2
Title of the Protocol: An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary safety of administration of aldoxorubicin in combination with ifosfamide in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiograms (ECHO) or multiple-gated acquisition (MUGA) scans, electrocardiogram (ECG) results, and weight. **Secondary Objectives:** The secondary objective of this study is to evaluate the activity of aldoxorubicin in combination with ifosfamide/mesna in this population, assessed by overall response rate, progression-free survival (PFS) and PFS at 4 and 6 months.	
Study Rationale and Significance: Aldoxorubicin is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models and in patients with soft tissue sarcomas when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months after treatment with single agent doxorubicin. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, as currently administered these regimens are quite toxic and have not significantly increased survival in these individuals. Aldoxorubicin in combination with a less toxic schedule for administering ifosfamide may improve the activity of this combination without increasing its toxicity as has been demonstrated for ifosfamide as a single agent.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Design and Methodology:

This is a phase 1b/2 open-label study evaluating the preliminary safety and activity of aldoxorubicin administered at either 170 or 250 mg/m^2 (125 and 185 mg/m^2 doxorubicin equivalents) intravenously (IV) on Day 1 every 28 days plus 1 gm/m^2/day **ifosfamide by continuous intravenous infusion for up to 10-14 days (based on tolerability) via a portable/ambulatory infusion pump using a central line such as port-a-cath or PICC line every** 28 days starting on Day 1 of each cycle, with equivalent dose of mesna via IV infusion daily with ifosfamide administration for 6 cycles. A subsequent dose level of aldoxorubicin may be administered if < 2 of 3 or < 3 of 6 subjects experience a DLT during Cycles 1 and 2. The subsequent dose level may not be initiated until all subjects have completed at least 2 cycles at the current dose level and approval is granted by the CytRx Medical Monitor. Treatment with granulocyte colony-stimulating factor (G-CSF) should be administered for all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E). **Note: aldoxorubicin, at higher doses, has been associated with >20% incidence of grade 3 or 4 neutropenia.** Subjects with response (CR, PR, or SD) to initial combination therapy may continue with aldoxorubicin alone every 21 days at the same dose as used with the combination until disease progression, unacceptable toxicity or withdrawal of consent.

The study is being expanded to further evaluate both the safety and efficacy observed to date with this combination. Seven subjects were enrolled in the aldoxorubicin (170 mg/m^2) + ifosfamide/mesna dose group without any dose-limiting toxicities. Similarly, 17 subjects have been enrolled in the aldoxorubicin (250 mg/m^2) + ifosfamide/mesna dose group without any dose-limiting toxicities. The most common Grade 3/4 adverse events across both cohorts have been neutropenia and anemia, both medically manageable. To date, there have been 6 subjects with confirmed partial responses and 10 subjects with stable disease across both dose groups. Ten additional subjects, for a total of 40 subjects, will be added across two cohorts: 1) 250 mg/m^2 aldoxorubicin + ifosfamide/mesna (10-14 days) dose group in previously untreated subjects (current study design), and 2) 250 mg/m^2 aldoxorubicin + ifosfamide/mesna at a dose of 1 gm/m^2 for up to 10 days in previously treated subjects.

Subjects will visit the study site every 28 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry and complete blood count [CBC]), vital signs, weight measurements, ECOG performance status and ECGs will be performed. All subjects will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically using either ECHO or MUGA scans. All subjects will have a CBC on Days 8, 11, 15, and 21 and a basic metabolic panel on Days 8, 15, and 21 at either the study site or at their local laboratory. Subjects will return to the study site on Days 4, 8, and 11 (except for those receiving up to 10 days of ifosfamide treatment) to have their ifosfamide infusion pump re-filled and receive intravenous anti-emetics and hydration therapy, if necessary. Between days 11-15, subjects will return to the study site to have their ifosfamide infusion pump turned off. For those subjects receiving ifosfamide for up to 10 days, they will return to the study site between days 10-11 to have their ifosfamide infusion pump turned off. Treatment with aldoxorubicin and ifosfamide/mesna will continue every 28 days for 6 cycles. Subjects with response (CR, PR, or SD) to initial combination therapy may continue with aldoxorubicin alone every 21 days at the same dose as used with the combination until disease progression is observed, unacceptable toxicity occurs, or consent is withdrawn.

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day 1 through week 32, and then every 12 weeks (±5 days) until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. For those subjects who stop treatment for reasons other than disease progression and who do not start another therapy, will be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. Progression-free survival, progression-free survival at 4 and 6 months will be monitored as other primary objectives.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age between 15-80 years, male or female.
2. For subjects without prior therapy, adjuvant or neoadjuvant chemotherapy (including doxorubicin) is allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. For subjects with prior therapy, no more than 2 prior regimens, and no prior exposure to ifosfamide. Subjects are not allowed to have been exposed to > 3 cycles or 225 mg/m^2 of doxorubicin or liposomal doxorubicin.
4. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma (including rhabdomyosarcoma, Ewing's sarcoma and mixed mesodermal sarcoma), chondrosarcoma or osteosarcoma of intermediate or high grade and gastrointestinal stromal tumors (GIST) (only in subjects that have progressed after receiving treatment with imatinib and sunitinib).
5. Capable of providing informed consent and complying with trial procedures.
6. ECOG performance status 0-2.
7. Life expectancy >12 weeks.
8. Measurable tumor lesions according to RECIST 1.1 criteria.
9. Women must not be able to become pregnant (eg post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
10. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 8 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and for 6 months after the final dose of study treatment.
11. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
12. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. For subjects without prior therapy, prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. For subjects with prior therapy, < 2 prior regimens or prior exposure to ifosfamide.
3. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
4. Palliative surgery and/or radiation treatment less than 30 days prior to enrollment.
5. Exposure to any investigational agent within 30 days of enrollment.
6. Current Stage 1 or 2 soft tissue sarcomas.
7. Current evidence/diagnosis of alveolar soft part sarcoma, dermatofibrosarcoma, Kaposi's sarcoma, clear cell sarcomas and unresectable low grade liposarcomas.
8. Anion gap > 16 meq/L or arterial blood pH < 7.30.
9. Central nervous system metastasis if symptomatic.
10. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for ≥ 5 years.
11. Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, albumin <2 gm/dL, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

12. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.
13. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
14. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation should be used with caution.
15. History or signs of active coronary artery disease with or without angina pectoris.
16. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
17. History of HIV infection.
18. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
19. Major surgery within 21 days prior to enrollment.
20. 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:
Up to 40 study subjects will be treated at US study centers.

Test Product, Dose and Mode of Administration:
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 IV infusion in Lactated Ringer's solution. Total dose of 170 or 250 mg/m^2 (125 and 185 mg/m^2 doxorubicin equivalents).

Ifosfamide 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 as a continuous IV infusion for up to 14 consecutive days.

Adjunctive Therapy, Dose and Mode of Administration:
Mesna Injection is a sterile, nonpyrogenic, aqueous solution of colorless to light pink appearance in clear glass multidose vials for intravenous administration. Mesna injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium, sodium hydroxide for pH adjustment and q.s with Water for Injection. Mesna injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. The solution has a pH range of 6.5 to 7.4.

Criteria for Evaluation:

Activity:
The following activity variables will be evaluated as noted:

- Progression-free survival
- Objective tumor response (RECIST 1.1 criteria)
- 4 and 6 month progression-free survival

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Safety:

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

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

Statistical Methods:

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

Activity:

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day1 through week 32, and then every 12 weeks (±5 days) until disease progression. For the estimation of progression-free a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 4 and 6 months.

Safety:

The safety data will be summarized by treatment group. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be summarized for each cohort. Adverse events, 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 groups. 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.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Day 1 of each Cycle	Day 4 of each Cycle**	Day 8 of each Cycle	Day 11 of each Cycle**	Day 10-11 of each Cycle[19]	Day 11-15 of each Cycle[20]	Day 21 of each Cycle	At end of every even Cycle	Every 8 weeks from Day 1 Cycle 1	Aldox Maintenance[21]	End of Treatment[13]	Every 2 or 3 mo.[12]
Signed informed consent	X												
Review inclusion/exclusion		X											
Medical history[1]	X												
Physical examination	X	X									X	X	X
Height (cm)	X												
Weight (kg)	X	X									X		
BSA calculation[2]		X									X		
Vital signs[3]	X	X									X	X	X
ECOG PS	X	X									X	X	
CT/ MRI scan / tumor measurements[4]	X[8a]									X[8]	X[8]	X[10]	X
ECG	X	X									X	X	X
ECHO (with ejection fraction) or MUGA	X								X[17]		X[22]	X	X
CBC w/differential & plts[5]	X	X		X	X		X	X			X[23]	X[11]	X
Coagulation tests (PT, PTT, INR)	X												
Serum chemistries [5, 6, 14]	X*	X		X[18]			X[18]	X[18]			X[24]	X[11]	
Urinalysis[7]	X											X[11]	
Serum/urine pregnancy test	X												
Aldoxorubicin and ifosfamide/mesna administration[15]		X											
Aldoxorubicin administration											X		
Re-fill infusion pump, provide IV anti-emetics and hydration therapy, if necessary			X	X	X								
Stop infusion pump						X	X						
Filgrastim or pegfilgrastim administration[16]						X	X						
Concomitant medications	X[9]	X									X	X	
Adverse events		X									X	X	

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1 (see Section 6 for details).
*Arterial blood gas test may be done, if needed, to confirm acid levels. **±2 days

CLINICAL PROTOCOL

TITLE:	**An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
PROTOCOL NUMBER:	**ALDOXORUBICIN-P1/2-STS-03**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**113,695**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd., Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-800-772-2215**
SAFETY FAX:	**1-888-772-6919**
SAFETY EMAIL:	**CHOsafety@praintl.com**
DATE OF PROTOCOL:	**June 30, 2014**
AMENDMENT 1:	**January 13, 2015**
AMENDMENT 2:	**September 1, 2015**
AMENDMENT 3:	**April 4, 2016**
AMENDMENT 4:	**September 30, 2016**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2
Title of the Protocol: An Open-Label Phase 1/2 Study to Investigate the Preliminary Safety and Activity of Aldoxorubicin plus Ifosfamide/Mesna in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary safety of administration of aldoxorubicin in combination with ifosfamide in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiograms (ECHO) or multiple-gated acquisition (MUGA) scans, electrocardiogram (ECG) results, and weight. **Secondary Objectives:** The secondary objective of this study is to evaluate the activity of aldoxorubicin in combination with ifosfamide/mesna in this population, assessed by overall response rate, progression-free survival (PFS) and PFS at 4 and 6 months.	
Study Rationale and Significance: Aldoxorubicin is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models and in patients with soft tissue sarcomas when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months after treatment with single agent doxorubicin. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, as currently administered these regimens are quite toxic and have not significantly increased survival in these individuals. Aldoxorubicin in combination with a less toxic schedule for administering ifosfamide may improve the activity of this combination without increasing its toxicity as has been demonstrated for ifosfamide as a single agent.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Design and Methodology:

This is a phase 1b/2 open-label study evaluating the preliminary safety and activity of aldoxorubicin administered at either 170 or 250 mg/m^2 (125 and 185 mg/m^2 doxorubicin equivalents) intravenously (IV) on Day 1 every 28 days plus 1 gm/m^2/day **ifosfamide by continuous intravenous infusion for up to 10-14 days (based on tolerability) via a portable/ambulatory infusion pump using a central line such as port-a-cath or PICC line every** 28 days starting on Day 1 of each cycle, with equivalent dose of mesna via IV infusion daily with ifosfamide administration for 6 cycles. A subsequent dose level of aldoxorubicin may be administered if < 2 of 3 or < 3 of 6 subjects experience a DLT during Cycles 1 and 2. The subsequent dose level may not be initiated until all subjects have completed at least 2 cycles at the current dose level and approval is granted by the CytRx Medical Monitor. Treatment with granulocyte colony-stimulating factor (G-CSF) should be administered for all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E). **Note: aldoxorubicin, at higher doses, has been associated with >20% incidence of grade 3 or 4 neutropenia.** Subjects with response (CR, PR, or SD) to initial combination therapy may continue with aldoxorubicin alone every 21 days at the same dose as used with the combination until disease progression, unacceptable toxicity or withdrawal of consent.

The study is being expanded to further evaluate both the safety and efficacy observed to date with this combination. Seven subjects were enrolled in the aldoxorubicin (170 mg/m^2) + ifosfamide/mesna dose group without any dose-limiting toxicities. Similarly, 17 subjects have been enrolled in the aldoxorubicin (250 mg/m^2) + ifosfamide/mesna dose group without any dose-limiting toxicities. The most common Grade 3/4 adverse events across both cohorts have been neutropenia and anemia, both medically manageable. To date, there have been 6 subjects with confirmed partial responses and 10 subjects with stable disease across both dose groups. Ten additional subjects, for a total of 40 subjects, will be added across two cohorts: 1) 250 mg/m^2 aldoxorubicin + ifosfamide/mesna (10-14 days) dose group in previously untreated subjects (current study design), and 2) 250 mg/m^2 aldoxorubicin + ifosfamide/mesna at a dose of 1 gm/m^2 for up to 10 days in previously treated subjects.

The aldoxorubicin 250 mg/m^2 + ifosfamide/mesna dose group is being expanded a second time to further assess the preliminary activity and safety of this combination. Thirty-one (31) subjects (22 first-line and 9 previously treated) have been enrolled in the aldoxorubicin (250 mg/m^2) + ifosfamide/mesna dose group without any dose-limiting toxicities. The most common Grade 3/4 adverse events have been neutropenia and anemia, both medically manageable. To date, there have been 4 subjects with confirmed partial responses and 13 subjects with stable disease in the 250 mg/mg^2 + ifosfamide/mesna dose group. Forty additional subjects, for a total of 80 subjects (73 in the 250 mg/m^2 + ifosfamide/mesna dose group), will be added equally (20 subjects per cohort) across two cohorts: 1) 250 mg/m^2 aldoxorubicin + ifosfamide/mesna (10-14 days) dose group in previously untreated subjects (current study design), and 2) 250 mg/m^2 aldoxorubicin + ifosfamide/mesna at a dose of 1 gm/m^2 for up to 10 days in previously treated subjects.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Design and Methodology (cont.):

Subjects will visit the study site every 28 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry and complete blood count [CBC]), vital signs, weight measurements, ECOG performance status and ECGs will be performed. All subjects will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. Cardiac function will also be followed periodically using either ECHO or MUGA scans. All subjects will have a CBC on Days 8, 11, 15, and 21 and a basic metabolic panel on Days 8, 15, and 21 at either the study site or at their local laboratory. Subjects will return to the study site on Days 4, 8, and 11 (except for those receiving up to 10 days of ifosfamide treatment) to have their ifosfamide infusion pump re-filled and receive intravenous anti-emetics and hydration therapy, if necessary. Between days 11-15, subjects will return to the study site to have their ifosfamide infusion pump turned off. For those subjects receiving ifosfamide for up to 10 days, they will return to the study site between days 10-11 to have their ifosfamide infusion pump turned off. Treatment with aldoxorubicin and ifosfamide/mesna will continue every 28 days for 6 cycles. Subjects with response (CR, PR, or SD) to initial combination therapy may continue with aldoxorubicin alone every 21 days at the same dose as used with the combination until disease progression is observed, unacceptable toxicity occurs, or consent is withdrawn.

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day 1 through week 32, and then every 12 weeks (±5 days) until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. For those subjects who stop treatment for reasons other than disease progression and who do not start another therapy, will be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. Progression-free survival, progression-free survival at 4 and 6 months will be monitored as other primary objectives.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P1/2-STS-03	**Phase of Development:** 1b/2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age between 15-80 years, male or female.
2. For subjects without prior therapy, adjuvant or neoadjuvant chemotherapy (including doxorubicin) is allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. For subjects with prior therapy, no more than 2 prior regimens, and no prior exposure to ifosfamide.
4. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma (including rhabdomyosarcoma, Ewing's sarcoma and mixed mesodermal sarcoma), chondrosarcoma or osteosarcoma of intermediate or high grade and gastrointestinal stromal tumors (GIST) (only in subjects that have progressed after receiving treatment with imatinib and sunitinib).
5. Capable of providing informed consent and complying with trial procedures.
6. ECOG performance status 0-2.
7. Life expectancy >12 weeks.
8. Measurable tumor lesions according to RECIST 1.1 criteria.
9. Women must not be able to become pregnant (eg post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
10. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 8 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and for 6 months after the final dose of study treatment.
11. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
12. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. For subjects without prior therapy, prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. For subjects with prior therapy, < 2 prior regimens or prior exposure to ifosfamide.
3. Palliative surgery and/or radiation treatment less than 30 days prior to enrollment.
4. Exposure to any investigational agent within 30 days of enrollment.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, dermatofibrosarcoma, Kaposi's sarcoma, clear cell sarcomas and unresectable low grade liposarcomas.
7. Anion gap > 16 meq/L or arterial blood pH < 7.30.
8. Central nervous system metastasis if symptomatic.
9. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for ≥ 5 years.
10. Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, albumin <2 gm/dL, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN.

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11. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) 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.
13. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation should be used with caution.
14. History or signs of active coronary artery disease with or without angina pectoris.
15. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
16. History of HIV infection.
17. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
18. Major surgery within 21 days prior to enrollment.
19. 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:
Up to 80 study subjects will be treated at US study centers.

Test Product, Dose and Mode of Administration:
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 IV infusion in Lactated Ringer's solution. Total dose of 170 or 250 mg/m^2 (125 and 185 mg/m^2 doxorubicin equivalents).

Ifosfamide 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 as a continuous IV infusion for up to 14 consecutive days.

Adjunctive Therapy, Dose and Mode of Administration:
Mesna Injection is a sterile, nonpyrogenic, aqueous solution of colorless to light pink appearance in clear glass multidose vials for intravenous administration. Mesna injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium, sodium hydroxide for pH adjustment and q.s with Water for Injection. Mesna injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. The solution has a pH range of 6.5 to 7.4.

Criteria for Evaluation:

Activity:
The following activity variables will be evaluated as noted:

- Progression-free survival
- Objective tumor response (RECIST 1.1 criteria)
- 4 and 6 month progression-free survival

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Safety:

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

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

Statistical Methods:

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

Activity:

Tumor response will be monitored every 8 weeks (±5 days) from Cycle 1-Day1 through week 32, and then every 12 weeks (±5 days) until disease progression. Objective response will be evaluated using the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1).[29] Changes (i.e., improvements) in tumor measurements from baseline values will be assigned a status of CR or PR. Objective response measurements will comprise the sum of CR plus PR. The overall response rate, as well as the rates for the individual categories of response (i.e., CR, PR, SD, and PD), will be estimated by the percentage of subjects achieving these criteria. For the estimation of progression-free survival a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 4 and 6 months.

Safety:

The safety data will be summarized by treatment group. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be summarized for each cohort. Adverse events, 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 groups. 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.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Day 1 of each Cycle	Day 4 of each Cycle**	Day 8 of each Cycle	Day 11 of each Cycle**	Day 10-11 of each Cycle[19]	Day 11-15 of each Cycle[20]	Day 21 of each Cycle	At end of every even Cycle	Every 8 weeks from Day 1 Cycle 1	Aldox Maintenance[21]	End of Treatment[13]	Every 2 or 3 mo.[12]
Signed informed consent	X												
Review inclusion/exclusion		X											
Medical history[1]	X												
Physical examination	X	X									X	X	X
Height (cm)	X												
Weight (kg)	X	X									X		
BSA calculation[2]		X									X		
Vital signs[3]	X	X									X	X	X
ECOG PS	X	X									X	X	
CT/ MRI scan / tumor measurements[4]	X[8a]									X[8]	X[8]	X[10]	X
ECG	X	X									X	X	X
ECHO (with ejection fraction) or MUGA	X								X[17]		X[22]	X	X
CBC w/differential & plts[5]	X	X		X	X		X	X			X[23]	X[11]	X
Coagulation tests (PT, PTT, INR)	X												
Serum chemistries [5, 6, 14]	X*	X		X[18]			X[18]	X[18]			X[24]	X[11]	
Urinalysis[7]	X											X[11]	
Serum/urine pregnancy test	X												
Aldoxorubicin and ifosfamide/mesna administration[15]		X											
Aldoxorubicin administration											X		
Re-fill infusion pump, provide IV anti-emetics and hydration therapy, if necessary			X	X	X								
Stop infusion pump						X	X						
Filgrastim or pegfilgrastim administration[16]						X	X						
Concomitant medications	X[9]	X									X	X	
Adverse events		X									X	X	

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1 (see Section 6 for details).
*Arterial blood gas test may be done, if needed, to confirm acid levels. **±2 days