CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy**

PROTOCOL NUMBER: **ALDOXORUBICIN-P2-SCLC-01**

STUDY DRUG: **Aldoxorubicin**

IND NUMBER: **75,478**

EUDRACT NUMBER: **2014-002189-64**

SPONSOR: **CytRx Corporation**
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South Korea: use email

SAFETY EMAIL: **safetydesk@psi-cro.com**

DATE OF PROTOCOL: **June 20, 2014**

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-SCLC-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to topotecan in subjects with metastatic small cell lung cancer (SCLC) who have relapsed or were refractory to prior 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), safety of aldoxorubicin compared to topotecan 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.	
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 SCLC who have failed prior chemotherapies have a poor prognosis with response rates of <10-25%, PFS of around 2-4 months and median OS of approximately 6-10 months, depending on the initial duration of response to first line treatment. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as topotecan (only approved agent in the US), topotecan plus platinum, cyclophosphamide + doxorubicin + vincristine (CAV) and amirubicin (not approved in US). However, these regimens can be quite toxic and have not significantly impacted either PFS or OS in these individuals. Aldoxorubicin may improve upon the activity of these drugs without an increase in toxicity as has been demonstrated in animal studies.	

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

Study Design and Methodology:

This is a phase 2b open-label study evaluating the efficacy and safety of aldoxorubicin administered at 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days compared to topotecan administered either IV at doses of 1.5 mg/m^2/day for 5 consecutive days starting on Day 1, and repeated every 21 days, or 4 mg/m^2 administered as a 30 min IV infusion on Days 1, 8 and 15 every 28 days. Subjects will be randomized 1:1 to receive either aldoxorubicin or topotecan. Pretreatment with granulocyte colony-stimulating factor (G-CSF) is permitted according to ASCO Guidelines (Appendix E).[31]

Subjects will visit the study site on Day 1 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, Eastern Cooperative Group performance status (ECOG PS) and ECGs will be performed on Day 1 of each cycle (for all subjects). They will have CBCs 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. Cardiac function will also be followed periodically (per schedule of evaluations) with ECHO for subjects receiving aldoxorubicin. Treatment will continue until tumor progression is observed, subject asks to withdraw, or unacceptable toxicity occurs.

Tumor response will be monitored at baseline, every 6 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.[22] Overall survival, PFS, and PFS at 4 and 6 months will be evaluated. Objective response rate (ORR; complete response [CR] and partial response [PR]), disease control rate (ORR plus stable disease [SD] at 4 months) and quality of life (ECOG PS) will be assessed.

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

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age ≥18 years male or female.
2. Histological confirmation of SCLC.
3. Relapsed or refractory to no more than 1 course of a systemic therapy regimen and is incurable by either surgery or radiation.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG PS 0-2.
6. Life expectancy >8 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.[22]
8. 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.)
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. 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 exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Prior treatment with topotecan.
3. Palliative surgery and/or radiation treatment < 21 days prior to date of randomization.
4. Exposure to any investigational agent within 30 days of date of randomization.
5. Exposure to any systemic chemotherapy within 21 days of date of randomization.
6. Active (symptomatic) central nervous system (CNS) metastasis.
7. 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 ≥3 years.
8. Laboratory values: Screening serum creatinine >1.5×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, albumin <2 gm/dL.
9. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (Appendix D).
10. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).

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

11. Baseline QTc >470 msec measured by Fridericia's formula (QTcF) 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.
12. History or signs of active coronary artery disease with angina pectoris within the last 6 months.
13. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
14. Known history of HIV infection.
15. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
16. Treatment with p-glycoprotein inhibitors such as cyclosporine A, elacridar, ketoconazole, ritonavir, saquinavir.
17. Major surgery within 30 days prior to date of randomization.
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:
Approximately 132 subjects with metastatic SCLC who have either not responded to or have progressed after treatment with no more than 1 prior systemic regimens will be randomized 1:1 (aldoxorubicin:topotecan) at approximately 30 study centers in the US, Europe, and Asia. The randomization will be stratified according to their initial PS (ECOG PS 0-1 vs 2), and whether they had relapsed < or > 90 days after completing their initial therapy.

Test Product 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 IV infusion in Lactated Ringer's solution. Total dose of 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent).

Topotecan:
Topotecan for Injection is supplied as a sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion (IVI). Each topotecan 4-mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride IVI or 5% Dextrose IVI prior to administration. Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- OS
- Objective tumor response (RECIST 1.1 criteria).[22]
- Disease control rate (ORR + SD at 4 months).
- Investigator assessment as measured by ECOG PS.

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

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.

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 approximately 6 months following the completion of enrollment of 132 subjects. Survival distributions will be estimated using the Kaplan-Meier method and the 2 groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

The final analysis of OS will be completed when 110 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the 2 groups will be compared using a two-sided log rank test.

Tumor response will be monitored at baseline, every 6 weeks from Cycle 1-Day 1 through week 33, and then every 12 weeks until disease progression. The percentage of subjects with CR or PR, or SD 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 less than 5, Fisher's exact test. Investigator reported outcomes as assessed by the ECOG PS will be analyzed using analysis of covariance.

Subjects in each group will be stratified according to their initial PS (ECOG PS 0-1 vs 2) and whether they had progressed in less than or greater than 90 days after their initial chemotherapy.

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 topotecan as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the topotecan group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 6.5 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 110 PFS events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 6 month follow-up period after enrollment of the last subject, approximately 132 subjects will be needed to achieve the total of 110 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. 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 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.

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 (repeat until off drug)	Day 15 (± 3 days) each Cycle	Weeks 27 & 33	End of Treatment[14]	Every 12 weeks[13]	Follow Up[12]
Signed ICF	X													
Review inclusion/exclusion	X	X												
Medical history[1]	X													
Physical examination	X	X	X	X	X	X	X	X	X			X[16]	X	
Height (cm)	X	X[2]												
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	
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[8]	X[8, 10]	X[8]	
ECG[18]	X	X	X	X	X	X	X	X	X			X[11]	X[11]	
ECHO (with ejection fraction)[19]	X		X		X		X		X			X	X	
CBC w/differential & plts[5, 20]	X	X[16]	X	X	X	X	X	X	X	X		X[11]	X[21]	
Serum chemistries[6, 20]	X	X[16]	X	X	X	X	X	X	X	X		X[11]		
Urinalysis[7]	X											X[11]		
Serum/urine pregnancy test	X													
Randomization		X[15]												
Aldoxorubicin administration[17]		X	X	X	X	X	X	X	X					
Topotecan		X	X	X	X	X	X	X	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		
Telephone follow-up														X

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

CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy**

PROTOCOL NUMBER: **ALDOXORUBICIN-P2-SCLC-01**

STUDY DRUG: **Aldoxorubicin**

IND NUMBER: **75,478**

EUDRACT NUMBER: **2014-002189-64**

SPONSOR: **CytRx Corporation**
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SAFETY EMAIL: **safetydesk@psi-cro.com**

DATE OF PROTOCOL: **June 20, 2014**

AMENDMENT 1: **September 10, 2014**

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-SCLC-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy	
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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 SCLC who have failed prior chemotherapies have a poor prognosis with response rates of <10-25%, PFS of around 2-4 months and median OS of approximately 6-10 months, depending on the initial duration of response to first line treatment. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as topotecan (only approved agent in the US), topotecan plus platinum, cyclophosphamide + doxorubicin + vincristine (CAV) and amirubicin (not approved in US). However, these regimens can be quite toxic and have not significantly impacted either PFS or OS in these individuals. Aldoxorubicin may improve upon the activity of these drugs without an increase in toxicity as has been demonstrated in animal studies.	

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

Study Design and Methodology:

This is a phase 2b open-label study evaluating the efficacy and safety of aldoxorubicin administered at 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days compared to topotecan administered either IV at doses of 1.5 mg/m^2/day for 5 consecutive days starting on Day 1, and repeated every 21 days, or 4 mg/m^2 administered as a 30 min IV infusion on Days 1, 8 and 15 every 28 days. Subjects will be randomized 1:1 to receive either aldoxorubicin or topotecan. Pretreatment with granulocyte colony-stimulating factor (G-CSF) is permitted according to ASCO Guidelines (Appendix E).[31]

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Tumor response will be monitored at baseline, every 6 weeks from Cycle 1-Day 1 through week 36, and then every 12 weeks until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[22] Overall survival, PFS, and PFS at 4 and 6 months will be evaluated. Objective response rate (ORR; complete response [CR] and partial response [PR]), disease control rate (ORR plus stable disease [SD] at 4 months) and quality of life (ECOG PS) will be assessed.

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

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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3. Relapsed or refractory to no more than 1 course of a systemic therapy regimen and is incurable by either surgery or radiation.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG PS 0-2.
6. Life expectancy >8 weeks.
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8. 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.)
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11. Accessibility to the site that ensures the subject will be able to keep all study-related appointments.

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Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Prior treatment with topotecan.
3. Palliative surgery and/or radiation treatment < 21 days prior to date of randomization.
4. Exposure to any investigational agent within 30 days of date of randomization.
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6. Active (symptomatic) central nervous system (CNS) metastasis.
7. 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 ≥3 years.
8. Laboratory values: Screening serum creatinine >1.5×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, albumin <2 gm/dL.
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Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-SCLC-01	**Phase of Development:** 2b

11. Baseline QTc >470 msec measured by Fridericia's formula (QTcF) 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.
12. History or signs of active coronary artery disease with angina pectoris within the last 6 months.
13. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
14. Known history of HIV infection.
15. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
16. Treatment with p-glycoprotein inhibitors such as cyclosporine A, elacridar, ketoconazole, ritonavir, saquinavir.
17. Major surgery within 30 days prior to date of randomization.
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:
Approximately 132 subjects with metastatic SCLC who have either not responded to or have progressed after treatment with no more than 1 prior systemic regimens will be randomized 1:1 (aldoxorubicin:topotecan) at approximately 30 study centers in the US and Europe. The randomization will be stratified according to their initial PS (ECOG PS 0-1 vs 2), and whether they had relapsed < or > 90 days after completing their initial therapy.

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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 IV infusion in Lactated Ringer's solution. Total dose of 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent).

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Topotecan for Injection is supplied as a sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion (IVI). Each topotecan 4-mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride IVI or 5% Dextrose IVI prior to administration. Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- PFS at 4 and 6 months
- OS
- Objective tumor response (RECIST 1.1 criteria)[22]
- Disease control rate (ORR + SD at 4 months)
- Investigator assessment as measured by ECOG PS

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

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

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 approximately 6 months following the completion of enrollment of 132 subjects. Survival distributions will be estimated using the Kaplan-Meier method and the 2 groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

The final analysis of OS will be completed when 110 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the 2 groups will be compared using a two-sided log rank test.

Tumor response will be monitored at baseline, every 6 weeks from Cycle 1-Day 1 through week 36, and then every 12 weeks until disease progression. The percentage of subjects with CR or PR, or SD 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 less than 5, Fisher's exact test. Investigator reported outcomes as assessed by the ECOG PS will be analyzed using analysis of covariance.

Subjects in each group will be stratified according to their initial PS (ECOG PS 0-1 vs 2) and whether they had progressed in less than or greater than 90 days after their initial chemotherapy.

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 topotecan as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the topotecan group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 6.5 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 110 PFS events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 6 month follow-up period after enrollment of the last subject, approximately 132 subjects will be needed to achieve the total of 110 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. 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 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.

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 (repeat until off drug)	Day 15 (± 1 day) each Cycle	End of Treatment[14]	Every 12 weeks[13]	Follow Up[12]
Signed ICF	X												
Review inclusion/exclusion	X	X											
Medical history[1]	X												
Physical examination	X	X	X	X	X	X	X	X	X		X[16]	X	
Height (cm)	X	X[2]											
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	
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[8, 10]	X[8]	
ECG[18]	X	X	X	X	X	X	X	X	X[18]		X[11]	X[11]	
ECHO (with ejection fraction)[19]	X		X		X		X		X[19]		X	X	
CBC w/differential & plts[5, 20]	X	X[16]	X	X	X	X	X	X	X	X	X[11]	X[21]	
Serum chemistries[6, 20]	X	X[16]	X	X	X	X	X	X	X	X	X[11]		
Urinalysis[7]	X										X[11]		
Serum/urine pregnancy test	X												
Randomization		X[15]											
Aldoxorubicin administration[17]		X	X	X	X	X	X	X	X				
Topotecan		X	X	X	X	X	X	X	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		
Telephone follow-up													X

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

CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy**

PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-SCLC-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**75,478**
EUDRACT NUMBER:	**2014-002189-64**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd., Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**United States: 1-877-412-8673** **Europe: +34 91 708 1250 ext. 41332** **or** **+34 619 085 583**
SAFETY FAX:	**United States: 1-877-853-3275** **Europe: + 34 91 307 60 47**
SAFETY EMAIL:	**drugsafety@pivotal.es**
DATE OF PROTOCOL:	**June 20, 2014**
AMENDMENT 1:	**September 10, 2014**
AMENDMENT 2:	**January 26, 2015**

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-SCLC-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to topotecan in subjects with metastatic small cell lung cancer (SCLC) who have relapsed or were refractory to prior 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), safety of aldoxorubicin compared to topotecan 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.	
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 SCLC who have failed prior chemotherapies have a poor prognosis with response rates of <10-25%, PFS of around 2-4 months and median OS of approximately 6-10 months, depending on the initial duration of response to first line treatment. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as topotecan (only approved agent in the US), topotecan plus platinum, cyclophosphamide + doxorubicin + vincristine (CAV) and amirubicin (not approved in US). However, these regimens can be quite toxic and have not significantly impacted either PFS or OS in these individuals. Aldoxorubicin may improve upon the activity of these drugs without an increase in toxicity as has been demonstrated in animal studies.	

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

Study Design and Methodology:

This is a phase 2b open-label study evaluating the efficacy and safety of aldoxorubicin administered at 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days compared to topotecan administered either IV at doses of 1.5 mg/m^2/day for 5 consecutive days starting on Day 1, and repeated every 21 days, or 4 mg/m^2 administered as a 30 min IV infusion on Days 1, 8 and 15 every 28 days. Subjects will be randomized 1:1 to receive either aldoxorubicin or topotecan. Treatment with granulocyte colony-stimulating factor (G-CSF) should be administered to all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E).[31] **Note: aldoxorubicin, at higher doses, has been associated with >20% incidence of grade 3 or 4 neutropenia.**

Subjects will visit the study site on Day 1 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry and complete blood count [CBC]), vital signs, weight measurements, Eastern Cooperative Group performance status (ECOG PS) and ECGs will be performed on Day 1 of each cycle (for all subjects). Subjects receiving aldoxorubicin will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. They will have CBCs and serum chemistries on Day 15 (± 1 day) of each cycle as well. Cardiac function will also be followed periodically (per schedule of evaluations) with ECHO for subjects receiving aldoxorubicin. Treatment will continue until tumor progression is observed, subject asks to withdraw, or unacceptable toxicity occurs.

Tumor response will be monitored at baseline, every 6 weeks (±5 days) from Cycle 1-Day 1 through week 36, and then every 12 weeks (±5 days) until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[22] Overall survival, PFS, and PFS at 4 and 6 months will be evaluated. Objective response rate (ORR; complete response [CR] and partial response [PR]), disease control rate (ORR plus stable disease [SD] at 4 months) and quality of life (ECOG PS) will be assessed.

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

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age ≥18 years male or female.
2. Histological confirmation of SCLC.
3. Relapsed or refractory to no more than 1 course of a systemic therapy regimen and is incurable by either surgery or radiation.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG PS 0-2.
6. Life expectancy >8 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.[22]
8. 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.)
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. 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 exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Prior treatment with topotecan.
3. Palliative surgery and/or radiation treatment < 21 days prior to date of randomization.
4. Exposure to any investigational agent within 30 days of date of randomization.
5. Exposure to any systemic chemotherapy within 21 days of date of randomization.
6. Active (symptomatic) central nervous system (CNS) metastasis.
7. 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 ≥3 years.
8. Laboratory values: Screening serum creatinine >1.5×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, albumin <2 gm/dL.
9. Anion gap > 16 meq/L or arterial blood pH < 7.30.
10. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (Appendix D).
11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).

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

12. Baseline QTc >470 msec measured by Fridericia's formula (QTcF) 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 angina pectoris within the last 6 months.
14. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
15. Known history of HIV infection.
16. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
17. Treatment with p-glycoprotein inhibitors such as cyclosporine A, elacridar, ketoconazole, ritonavir, saquinavir.
18. Major surgery within 30 days prior to date of randomization.
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:
Approximately 132 subjects with metastatic SCLC who have either not responded to or have progressed after treatment with no more than 1 prior systemic regimens will be randomized 1:1 (aldoxorubicin:topotecan) at approximately 40 study centers in the US and Europe. The randomization will be stratified according to their initial PS (ECOG PS 0-1 vs 2), and whether they had relapsed < or > 90 days after completing their initial therapy.

Test Product 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 IV infusion in Lactated Ringer's solution. Total dose of 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent).

Topotecan:
Topotecan for Injection is supplied as a sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion (IVI). Each topotecan 4-mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride IVI or 5% Dextrose IVI prior to administration. Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- PFS at 4 and 6 months
- OS
- Objective tumor response (RECIST 1.1 criteria)[22]
- Disease control rate (ORR + SD at 4 months)
- Investigator assessment as measured by ECOG PS

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

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

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 approximately 6 months following the completion of enrollment of 132 subjects. Survival distributions will be estimated using the Kaplan-Meier method and the 2 groups will be compared using a two-sided log rank test at the α=0.05 level of significance.

The final analysis of OS will be completed when 110 OS events have occurred. Survival distributions will be estimated using the Kaplan-Meier method and the 2 groups will be compared using a two-sided log rank test.

Tumor response will be monitored at baseline, every 6 weeks (±5 days) from Cycle 1-Day 1 through week 36, and then every 12 weeks (±5 days) until disease progression. The percentage of subjects with CR or PR, or SD 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 less than 5, Fisher's exact test. Investigator reported outcomes as assessed by the ECOG PS will be analyzed using analysis of covariance.

Subjects in each group will be stratified according to their initial PS (ECOG PS 0-1 vs 2) and whether they had progressed in less than or greater than 90 days after their initial chemotherapy.

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 topotecan as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the topotecan group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 6.5 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 110 PFS events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 6 month follow-up period after enrollment of the last subject, approximately 132 subjects will be needed to achieve the total of 110 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. 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 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.

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 (repeat until off drug)	Day 15 (± 1 day) each Cycle	End of Treatment[14]	Every 12 weeks[13]	Follow Up[12]
Signed ICF	X												
Review inclusion/exclusion	X	X											
Medical history[1]	X												
Physical examination	X	X	X	X	X	X	X	X	X		X	X	
Height (cm)	X	X[2]											
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	
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[8, 10]	X[8]	
ECG[18]	X	X	X	X	X	X	X	X	X[18]		X[11]	X[11]	
ECHO (with ejection fraction)[19]	X		X		X		X		X[19]		X	X	
CBC w/differential & plts[5, 20]	X	X[16]	X	X	X	X	X	X	X	X	X[11]	X[21]	
Serum chemistries[6, 20]	X*	X[16]	X	X	X	X	X	X	X	X	X[11]		
Urinalysis[7]	X										X[11]		
Serum/urine pregnancy test	X												
Randomization		X[15]											
Aldoxorubicin administration[17]		X	X	X	X	X	X	X	X				
Topotecan		X	X	X	X	X	X	X	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		
Telephone follow-up													X

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

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

CLINICAL PROTOCOL

TITLE: **A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy**

PROTOCOL NUMBER:	**ALDOXORUBICIN-P2-SCLC-01**
STUDY DRUG:	**Aldoxorubicin**
IND NUMBER:	**75,478**
EUDRACT NUMBER:	**2014-002189-64**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd., Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**United States: 1-877-412-8673** **Europe: +34 91 708 1250 ext. 41332** **or** **+34 619 085 583**
SAFETY FAX:	**United States: 1-877-853-3275** **Europe: + 34 91 307 60 47**
SAFETY EMAIL:	**drugsafety@pivotal.es**
DATE OF PROTOCOL:	**June 20, 2014**
AMENDMENT 1:	**September 10, 2014**
AMENDMENT 2:	**January 26, 2015**
AMENDMENT 3:	**February 17, 2016**

Protocol Synopsis

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: ALDOXORUBICIN-P2-SCLC-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Topotecan in Subjects with Metastatic Small Cell Lung Cancer Who Either Relapsed or Were Refractory to Prior Chemotherapy	
Primary Objective: The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to topotecan in subjects with metastatic small cell lung cancer (SCLC) who have relapsed or were refractory to prior 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), safety of aldoxorubicin compared to topotecan 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.	
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 SCLC who have failed prior chemotherapies have a poor prognosis with response rates of <10-25%, PFS of around 2-4 months and median OS of approximately 6-10 months, depending on the initial duration of response to first line treatment. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as topotecan (only approved agent in the US), topotecan plus platinum, cyclophosphamide + doxorubicin + vincristine (CAV) and amirubicin (not approved in US). However, these regimens can be quite toxic and have not significantly impacted either PFS or OS in these individuals. Aldoxorubicin may improve upon the activity of these drugs without an increase in toxicity as has been demonstrated in animal studies.	

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

Study Design and Methodology:

This is a phase 2b open-label study evaluating the efficacy and safety of aldoxorubicin administered at 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent) intravenously on Day 1 every 21 days compared to topotecan administered either IV at doses of 1.5 mg/m^2/day for 5 consecutive days starting on Day 1, and repeated every 21 days, or 4 mg/m^2 administered as a 30 min IV infusion on Days 1, 8 and 15 every 28 days. Subjects will be randomized 1:1 to receive either aldoxorubicin or topotecan. Treatment with granulocyte colony-stimulating factor (G-CSF) should be administered to all subjects as per investigator's clinical judgment or according to ASCO Guidelines (Appendix E).[31] **Note: aldoxorubicin, at higher doses, has been associated with >20% incidence of grade 3 or 4 neutropenia.**

Subjects will visit the study site on Day 1 of each cycle. Safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry and complete blood count [CBC]), vital signs, weight measurements, Eastern Cooperative Group performance status (ECOG PS) and ECGs will be performed on Day 1 of each cycle (for all subjects). Subjects receiving aldoxorubicin will have blood drawn for serum electrolytes to evaluate the anion gap prior to each drug administration. They will have CBCs and serum chemistries on Day 15 (± 1 day) of each cycle as well. Cardiac function will also be followed periodically (per schedule of evaluations) with ECHO for subjects receiving aldoxorubicin. Treatment will continue until tumor progression is observed, subject asks to withdraw, or unacceptable toxicity occurs.

Tumor response will be monitored at baseline, every 6 weeks (± 5 days) from Cycle 1-Day 1 through week 36, and then every 12 weeks (± 5 days) until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[22] Overall survival, PFS, and PFS at 4 and 6 months will be evaluated. Objective response rate (ORR; complete response [CR] and partial response [PR]), disease control rate (ORR plus stable disease [SD] at 4 months) and quality of life (ECOG PS) will be assessed.

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

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age ≥18 years male or female.
2. Histological confirmation of SCLC.
3. Relapsed or refractory to no more than 1 course of a systemic therapy regimen and is incurable by either surgery or radiation.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG PS 0-2.
6. Life expectancy >8 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.[22]
8. 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.)
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.
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11. 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 exposure to >375 mg/m^2 of doxorubicin or liposomal doxorubicin.
2. Prior treatment with topotecan.
3. Palliative surgery and/or radiation treatment < 14 days prior to date of randomization.
4. Exposure to any investigational agent within 30 days of date of randomization.
5. Exposure to any systemic chemotherapy within 21 days of date of randomization.
6. Active (symptomatic) central nervous system (CNS) metastasis.
7. 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 ≥3 years.
8. Laboratory values: Screening serum creatinine >1.5×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, albumin <2 gm/dL.
9. Anion gap >16 meq/L or arterial blood pH <7.30.
10. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) guidelines (Appendix D).
11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).

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

12. Baseline QTc >470 msec measured by Fridericia's formula (QTcF) 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 angina pectoris within the last 6 months.
14. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution's lower limit of predicted normal.
15. Known history of HIV infection.
16. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
17. Treatment with p-glycoprotein inhibitors such as cyclosporine A, elacridar, ketoconazole, ritonavir, saquinavir.
18. Major surgery within 30 days prior to date of randomization.
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:
Approximately 132 subjects with metastatic SCLC who have either not responded to or have progressed after treatment with no more than 1 prior systemic regimens will be randomized 1:1 (aldoxorubicin:topotecan) at approximately 40 study centers in the US and Europe. The randomization will be stratified according to their initial PS (ECOG PS 0-1 vs 2), and whether they had relapsed < or > 90 days after completing their initial therapy.

Test Product 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 an approximate 30 minute IV infusion in Lactated Ringer's solution. Total dose of 230 mg/m^2 (170 mg/m^2 doxorubicin equivalent).

Topotecan:
Topotecan for Injection is supplied as a sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion (IVI). Each topotecan 4-mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride IVI or 5% Dextrose IVI prior to administration. Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- PFS
- PFS at 4 and 6 months
- OS
- Objective tumor response (RECIST 1.1 criteria)[22]
- Disease control rate (ORR + SD at 4 months)
- Investigator assessment as measured by ECOG PS

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

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

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 110 PFS events have occurred, approximately 6 months following the completion of enrollment of 132 subjects. Survival distributions will be estimated using the Kaplan-Meier method and the 2 groups will be compared using a two-sided, unstratified log rank test at the α=0.05 level of significance.

Tumor response will be monitored at baseline, every 6 weeks (± 5 days) from Cycle 1-Day 1 through week 36, and then every 12 weeks (± 5 days) until disease progression. The percentage of subjects with CR or PR, or SD 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 less than 5, Fisher's exact test. Investigator reported outcomes as assessed by the ECOG PS will be analyzed using analysis of covariance.

Subjects in each group will be stratified according to their initial PS (ECOG PS 0-1 vs 2) and whether they had progressed in less than or greater than 90 days after their initial chemotherapy.

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 topotecan as treatment for patients that have relapsed or not responded to first line therapies, it is estimated that the median PFS for the topotecan group will be 3.5 months and that the median PFS for the aldoxorubicin group will be 6.5 months. Based on the use of a two-sided log rank test at the α=0.05 level of significance, a total of 110 PFS events will be required for 90% power to detect this difference. Assuming an 18 month accrual period and a 6 month follow-up period after enrollment of the last subject, approximately 132 subjects will be needed to achieve the total of 110 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. 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 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.

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 (repeat until off drug)	Day 15 (± 1 day) each Cycle	End of Treatment[14]	Every 12 weeks[13]	Follow Up[12]
Signed ICF	X												
Review inclusion/exclusion	X	X											
Medical history[1]	X												
Physical examination	X	X	X	X	X	X	X	X	X		X	X	
Height (cm)	X	X[2]											
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	
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[8, 10]	X[8]	
ECG[18]	X	X	X	X	X	X	X	X	X[18]		X[11]	X[11]	
ECHO (with ejection fraction)[19]	X		X		X		X		X[19]		X[22]	X	
CBC w/differential & plts[5, 20]	X	X[16]	X	X	X	X	X	X	X	X	X[11]	X[21]	
Serum chemistries[6, 20]	X*	X[16]	X	X	X	X	X	X	X	X	X[11]		
Urinalysis[7]	X										X[11]		
Serum/urine pregnancy test	X												
Randomization		X[15]											
Aldoxorubicin administration[17]		X	X	X	X	X	X	X	X				
Topotecan		X	X	X	X	X	X	X	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		
Telephone follow-up													X

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

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