CLINICAL PROTOCOL

TITLE:	**A Multicenter, Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) in Subjects with Advanced or Unresectable Pancreatic Ductal Carcinoma Whose Tumors Have Progressed Following Prior Treatment with Gemcitabine and Fluoropyrimidine-Based Chemotherapy**
PROTOCOL NUMBER:	**INNO-206-P2-PDA-01**
STUDY DRUG:	**INNO-206**
IND NUMBER:	**114,751**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd, Suite 650** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**1-310-674-6711**
SAFETY FAX:	**1-310-826-2672**
DATE OF PROTOCOL:	**March 15, 2012**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2
Title of the Protocol: A Multicenter, Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) in Subjects with Advanced or Unresectable Pancreatic Ductal Carcinoma Whose Tumors Have Progressed Following Prior Treatment with Gemcitabine and Fluoropyrimidine-Based Chemotherapy	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of INNO-206 to subjects with advanced or unresectable pancreatic ductal carcinoma who have failed 2 courses of chemotherapy (gemcitabine-containing and fluoropyrimidine-containing regimens) as measured by objective tumor response (RECIST 1.1 criteria), disease control (complete and partial responses, and stable disease at 4 months), progression-free and overall survival. **Secondary Objectives:** The secondary objectives of this study are to evaluate the safety of INNO-206 in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, ECHO evaluations, electrocardiogram (ECG) results, and weight, the pharmacokinetic profile of INNO-206, evaluation of secreted protein acidic and rich in cysteine (SPARC) in tumor specimens, changes in PET-CT scans and changes in CA 19-9 expression during treatment.	
Study Rationale and Significance: INNO-206 is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable pancreatic ductal carcinomas (PDA) who have failed prior chemotherapy with gemcitabine regimens have an extremely poor prognosis with progression-free survival of around 13 weeks and median overall survival of approximately 20 weeks after second line chemotherapy. Recent studies suggest that albumin may be preferentially concentrated in pancreatic cancers that appear to be starved for this protein. Thus, any molecule attached to albumin would also collect inside the tumor. Based on its postulated mechanism of action, INNO-206 may improve the activity of doxorubicin without increasing its toxicity, as has been demonstrated in animal studies, and induce enhanced anti-tumor efficacy.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

Study Design and Methodology:

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of INNO-206 administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously (IV) on Day 1 every 21 days for up to 8 consecutive cycles.

Tumor response (complete and partial response and stable disease) will be monitored at Screening, then every 8 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and treatment will continue every 21 days until tumor progression is observed, 8 cycles of treatment are completed or unacceptable toxicity occurs. Progression-free survival [PFS], stable disease at 4 months and overall survival [OS] will be monitored as other primary objectives. PET/CT will be performed at Baseline and Week 9 to determine change in tumor metabolic activity, and CA 19-9 will be determined serially to assess potential tumor reduction. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, ECOG performance status and ECGs will be performed. Cardiac function will also be followed periodically using ECHOs.

Name of Sponsor/Company: CytRx Corporation

Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic pancreatic ductal adenocarcinoma.
3. Cancer progression after treatment with one gemcitabine and one fluoropyrimidine-containing chemotherapy regimen.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-1.
6. Life expectancy ≥8 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. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
10. Geographic accessibility to the site.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
2. Palliative surgery and/or radiation treatment less than 4 weeks prior to Randomization.
3. Exposure to any investigational agent within 30 days of Randomization.
4. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of Screening Visit).
5. History of other malignancies (except cured basal cell carcinoma, superficial bladder cancer or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥5 years.
6. 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, absolute lymphocyte count <1000/mm^3, hematocrit level <27% for females or <30% for males, or coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5×ULN, serum albumin ≤2.8 g/dL.
7. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.
8. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
9. History or signs of active coronary artery disease with or without angina pectoris.
10. Serious myocardial dysfunction defined scintigraphically (MUGA, myocardial scintigram) or ultrasound-determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
11. History of HIV infection.
12. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

13. Major surgery within 4 weeks prior to Randomization.
14. Substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
15. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 27 subjects will be enrolled at up to 5 study centers in the United States.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of INNO-206 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 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Reference Therapy, Dose and Mode of Administration:
None

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- Progression-free survival
- Overall survival
- Objective tumor response (RECIST 1.1 criteria)
- Stable disease at 4 months
- Reduction of CA 19-9 concentration
- Decreased uptake at 9 weeks on PET/CT

Safety:
The following safety variables will be assessed over 50 weeks or until removal from the study:
- Adverse events
- 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

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

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

Efficacy:
Tumor response will be monitored monthly until disease progression. For the estimation of progression-free and overall survival a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at monthly intervals. PET/CT scans will be performed at baseline and 9 weeks (prior to cycle 4 of therapy). CA 19-9 will be measured at every cycle.

Safety:
The safety data will be summarized for all subjects. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be evaluated. 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 regimen. Descriptive evaluation denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	Cycles 2-8	Cycles 3, 5, 7, and post-Cycle 8	Week 9	Every 2 months after Cycle 8	End of Study or Early Termination	Follow-up[14]
Signed informed consent	X							
Review inclusion/exclusion	X	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	
ECOG PS	X	X	X				X	
CT/ MRI scan / tumor measurements[4]	X			X[8]		X		
18F-FDG PET	X				X			
PET/CT[12]	X[10]							
ECG	X	X	X			X	X	
ECHO (with ejection fraction)	X		X[13]			X	X	
CBC w/differential & plts[5]	X	X	X			X	X	
Serum chemistries[5,6] & CA 19-9	X	X	X			X	X	
Urinalysis[7]	X						X	
Serum troponin	X	X[10]	X			X	X	
Serum/urine pregnancy test	X							
INNO-206 administration		X	X					
Pharmacokinetics[15]		X						
Concomitant medications[9]	X	X	X			X	X	
Adverse events[11]	X	X	X				X	
Telephone follow-up[14]								X

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

CLINICAL PROTOCOL

TITLE:	**A Multicenter, Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) in Subjects with Advanced or Unresectable Pancreatic Ductal Carcinoma Whose Tumors Have Progressed Following Prior Treatment with Gemcitabine and Fluoropyrimidine-Based Chemotherapy**
PROTOCOL NUMBER:	**INNO-206-P2-PDA-01**
STUDY DRUG:	**INNO-206**
IND NUMBER:	**114,751**
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SAFETY HOTLINE:	**1-310-674-6711**
SAFETY FAX:	**1-888-726-8416**
DATE OF PROTOCOL:	**March 15, 2012**
AMENDMENT 1:	**April 3, 2012**

SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2
Title of the Protocol: A Multicenter, Open-Label Pilot Phase 2 Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) in Subjects with Advanced or Unresectable Pancreatic Ductal Carcinoma Whose Tumors Have Progressed Following Prior Treatment with Gemcitabine and Fluoropyrimidine-Based Chemotherapy	
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Study Rationale and Significance: INNO-206 is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable pancreatic ductal carcinomas (PDA) who have failed prior chemotherapy with gemcitabine regimens have an extremely poor prognosis with progression-free survival of around 13 weeks and median overall survival of approximately 20 weeks after second line chemotherapy. Recent studies suggest that albumin may be preferentially concentrated in pancreatic cancers that appear to be starved for this protein. Thus, any molecule attached to albumin would also collect inside the tumor. Based on its postulated mechanism of action, INNO-206 may improve the activity of doxorubicin without increasing its toxicity, as has been demonstrated in animal studies, and induce enhanced anti-tumor efficacy.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

Study Design and Methodology:

This is a phase 2 open-label, pilot study evaluating the preliminary efficacy and safety of INNO-206 administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously (IV) on Day 1 every 21 days for up to 8 consecutive cycles.

Tumor response (complete and partial response and stable disease) will be monitored at Screening, then prior to cycles 3, 5 and 7, 3 weeks after cycle 8, then every 2 months to month 8 and every 3 months to tumor progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and treatment will continue every 21 days until tumor progression is observed, 8 cycles of treatment are completed or unacceptable toxicity occurs. Progression-free survival [PFS], stable disease at 4 months and overall survival [OS] will be monitored as other primary objectives. PET/CT will be performed at Baseline and Week 9 to determine change in tumor metabolic activity, and CA 19-9 will be determined serially to assess potential tumor reduction. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, ECOG performance status and ECGs will be performed. Cardiac function will also be followed periodically using ECHOs.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Age ≥18 years of age; male or female.
2. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic pancreatic ductal adenocarcinoma.
3. Cancer progression after treatment with one gemcitabine and one fluoropyrimidine-containing chemotherapy regimen.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-1.
6. Life expectancy ≥8 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. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
10. Geographic accessibility to the site.

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Subjects meeting the following criteria will not be enrolled:

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4. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of Screening Visit).
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7. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.
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9. History or signs of active coronary artery disease with or without angina pectoris.
10. Serious myocardial dysfunction ultrasound-determined, with absolute left ventricular ejection fraction (LVEF) <45% of predicted.
11. History of HIV infection.
12. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

13. Major surgery within 4 weeks prior to Randomization.
14. Substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
15. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
Up to 27 subjects will be enrolled at up to 5-7 study centers in the United States.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of INNO-206 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 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Reference Therapy, Dose and Mode of Administration:
None

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:
- Progression-free survival
- Overall survival
- Objective tumor response (RECIST 1.1 criteria)
- Stable disease at 4 months
- Reduction of CA 19-9 concentration
- Decreased uptake at 9 weeks on FDG PET/CT

Safety:
The following safety variables will be assessed over 50 weeks or until removal from the study:
- Adverse events
- 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

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-PDA-01	**Phase of Development:** 2

Statistical Methods:

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

Efficacy:

Tumor response will be monitored every eight weeks until disease progression. For the estimation of progression-free and overall survival a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at monthly intervals. FDG PET/CT scans will be performed at baseline and 9 weeks (prior to cycle 4 of therapy). CA 19-9 will be measured at every cycle.

Safety:

The safety data will be summarized for all treated subjects. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be evaluated. 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 regimen. Descriptive evaluation denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	Cycles 2-8	Cycles 3, 5, 7, and post-Cycle 8	Week 9	Every 2 months after Cycle 8	End of Study or Early Termination	Follow-up[14]
Signed informed consent	X							
Review inclusion/exclusion	X	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	
ECOG PS	X	X	X				X	
CT/ MRI scan / tumor measurements[4]	X			X[8]		X		
FDG PET[12]	X				X			
ECG	X	X	X			X	X	
ECHO (with ejection fraction)	X		X[13]			X	X	
CBC w/differential & plts[5]	X	X	X			X	X	
Serum chemistries[5,6] & CA 19-9	X	X	X			X	X	
Urinalysis[7]	X						X	
Serum troponin	X	X[10]	X			X	X	
Serum/urine pregnancy test	X							
INNO-206 administration		X	X					
Obtain tumor tissue sample[15]		X						
Concomitant medications[9]	X	X	X			X	X	
Adverse events[11]	X	X	X				X	
Telephone follow-up[14]								X

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