CLINICAL PROTOCOL

TITLE:	**A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
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STUDY DRUG:	**INNO-206**
IND NUMBER:	**113,695**
EUDRACT NUMBER:	**2011-004927-11**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**Toll-free: 1-877-462-0134**
SAFETY FAX:	**Toll-free: 1-877-464-7787**
DATE OF PROTOCOL:	**November 14, 2011**
AMENDMENT 1:	**December 16, 2011**
AMENDMENT 2:	**April 15, 2012**

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PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma

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

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

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: _____

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

Date: _____

1. SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of INNO-206 compared to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by progression-free survival, progression-free survival at 4 and 6 months, tumor response and overall survival. **Secondary Objectives:** The secondary objective of this study is to evaluate the safety of INNO-206 compared to doxorubicin in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, multiple-gated acquisition (MUGA) scans/cardiac ultrasound evaluations, electrocardiogram (ECG) results, and weight.	
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 soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months. Three-year survival rates as high as 30% have been observed in some clinical studies. 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, these regimens are quite toxic and have not significantly increased survival in these individuals. INNO-206 may improve the activity of doxorubicin without increasing its toxicity as has been demonstrated in animal studies.	

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

Study Design and Methodology:

This is a phase 2b open-label 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 6 consecutive cycles compared to doxorubicin administered at 75 mg/m^2 for up to 6 consecutive cycles. Subjects will be randomized 2:1 to receive either INNO-206 or doxorubicin.

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 either MUGA scans or cardiac ultrasounds. Treatment will continue every 21 days until tumor progression is observed, 6 cycles of treatment are completed or unacceptable toxicity occurs.

Tumor response will be monitored every 6 weeks from Cycle 1-Day 1 during treatment, at End of Treatment, 2 months following the End of Treatment scan (for those subjects completing 6 cycles), and then every 3 months until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. For those subjects that leave the study prior to completing Cycle 6, and who do not start another therapy, they can be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. However, if a subject receives another therapy, they should only be followed for overall survival [OS]. Progression-free survival [PFS], progression-free survival at 4 and 6 months and OS will be monitored as other primary objectives.

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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 (US only), and 18-80 (rest of world (ROW)), 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 of intermediate or high grade.
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. 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 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 4 weeks prior to Randomization.
4. Exposure to any investigational agent within 30 days of Randomization.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma, Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas and unresectable low grade liposarcomas.
7. Central nervous system metastasis
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, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN, and albumin <2.0 g/dL.
10. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.

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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 3 weeks prior to 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:
One hundred and five (105) study subjects will be randomized 2:1 (INNO-206:doxorubicin) at approximately 30 study centers in the United States (US), Hungary, Romania, Ukraine, Russia, India, and Australia. Up to 32 subjects may be enrolled in India, with the remaining subjects distributed in the other locations.

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:
Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. Prepare IV infusion per the package insert (see the Study Reference Manual).

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)
- 4 and 6 month progression-free survival

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/cardiac ultrasound evaluations, ECG results and laboratory test results
- Use of concomitant medications

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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 according to the treatment group to which they were originally assigned.

Efficacy:

Tumor response will be monitored every 6 weeks from Cycle 1-Day1 during treatment, at End of Treatment, 2 months following the End of Treatment scan (for those subjects completing 6 cycles), then every 3 months 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 4 and 6 months.

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.

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{expol}	AUC calculated from time 0 to infinity minus AUC calculated from time 0 to last time point
AUC_{inf}	AUC calculated from time 0 to infinity
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CHF	congestive heart failure
Cl	clearance
Cl_{obs}	total body clearance
C_{max}	peak plasma concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	dose limiting toxicity
DOX	doxorubicin
DOXO-EMCH	(6-maleimidocaproyl) hydrazone derivative of doxorubicin
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EP	etoposide and cisplatin (chemotherapy combination)
EPR (effect)	enhanced permeability and retention of macromolecules
ES	extensive stage [disease]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIST	gastrointestinal stromal tumor
GLP	Good Laboratory Practice
HSA	human serum albumin
HPLC	high performance liquid chromatography
ICD	Informed Consent Document
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee

IND	Investigational New Drug (application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
IVI	intravenous infusion
LC	liquid chromatography
LOC	loss of consciousness
LD	longest diameter
LDH	lactate dehydrogenase
LS	limited-stage [disease]
MRI	magnetic resonance imaging
MRT	mean residence time after administration
MS	mass spectrometry
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetic
PR	partial response
PS	performance status (ECOG scale)
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria In Solid Tumors
RENCA	renal cell carcinoma (cell line)
ROW	rest of world
RP2D	recommended Phase II dose
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
T_{max}	time to peak concentration
$t_{1/2}$	half life
TTP	time to progression
ULN	upper limit of normal
US	United States
V_{SS}	steady state volume of distribution
V_{z_obs}	apparent volume of distribution
WHO	World Health Organization
WNL	within normal limits

2. BACKGROUND

Soft tissue sarcomas comprise a group of relatively uncommon tumors that possess distinct histological and morphological characteristics. These tumors may arise in a variety of sites that include soft tissues, skin muscle, and internal organs, with differentiation patterns similar to smooth muscle, adipocyte, striated muscle, endothelium, or fibrocyte, all mesenchymal in origin. The extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%) account for the sites where these tumors develop. The 3 major histological types of soft tissue sarcomas are leiomyosarcomas, malignant fibrous histiocytomas and liposarcomas. Most tumors arise in the soft tissues, including the heart, with the skin, uterus, and retroperitoneum following.[1]

Recent estimates indicate that there will be 10,980 new cases of soft tissue sarcomas diagnosed in the United States (US) in 2011, with almost 4,000 deaths.[2] Incidence rates rise exponentially with age with a modest peak in childhood due primarily to the increased development of embryonal rhabdomyosarcoma. Peak rates of the other soft tissue sarcomas occur in individuals ≥75 years, except for uterine leiomyosarcomas, which reach peak incidence in women between the ages of 40 and 50 years. In general, African-Americans have a higher rate of soft tissue sarcoma development than do Caucasians.[3]

Treatment and prognosis for adults with soft tissue sarcomas depend on a variety of factors that include the histological grade of the tumor, grade of the tumor, size (≥5 cm) and the subject's age. Large, poorly differentiated tumors in subjects over 60 years are associated with relatively poorer outcomes.[4-7]

Surgery is the mainstay for treating soft tissue sarcomas in any site. While amputation of extremities was the previous approach towards curatively treating localized soft tissue sarcomas, the current recommendations call for local excision with as wide margins as possible to preserve the function of the extremity. Even high-grade sarcomas can be surgically treated when combined with pre- and post-operative radiation therapy.[8,9]

The role of chemotherapy for high-grade stage 3 or 4 soft tissue sarcomas is unclear. Although subjects have achieved a higher response rate using combinations of ifosfamide, doxorubicin, dacarbazine, and mesna compared with doxorubicin and dacarbazine alone (33% vs 17%), this increased response rate has not translated into a survival benefit. Further, the toxicity of this regimen, especially in older subjects, has created safety concerns that reduce the therapeutic options for this age sector. However, doxorubicin, either alone or in combination with ifosfamide, is still considered the mainstay chemotherapeutic agent for the treatment of advanced, unresectable tumors.[10-14]

Doxorubicin

Doxorubicin is a highly potent antitumor agent that is among one of the most active antineoplastic drugs developed to date and is used in the treatment of hematological and solid cancers such as breast and ovarian carcinoma, sarcoma, and many other solid tumors.[15,16] The clinical application of this anthracycline is, however, limited by its toxic dose-related side effects that include bone marrow toxicity, gastrointestinal disorders, stomatitis, alopecia, acute and cumulative cardiotoxicity as well as extravasation.[15] Bone marrow suppression is generally dose limiting; myelosuppression and thrombocytopenia are most prominent after each course of treatment with maximum toxicity after 7 to 10 days and a rapid recovery thereafter. Of special concern is the cumulative cardiotoxicity (cardiomyopathy and congestive heart failure [CHF]) that is irreversible, reaching more than 5% once cumulative doses of doxorubicin exceed 550 mg/m^2. [17,18] This toxicity is of special concern in curative oncology when treating hematological cancers as well as in the adjuvant

setting, eg in the treatment of breast cancer. Newer data have shown that the critical cumulative dose is even lower than the "old" threshold of 5% at 550 mg/m^2.[19,20]

2.1 INNO-206

In order to circumvent these limitations and to improve the therapeutic potential of anthracyclines, several drug delivery systems such as liposomal formulations and prodrugs have been investigated.[21] A macromolecular prodrug strategy based on 2 features has been investigated for doxorubicin: (1) rapid and selective binding of thiol-reactive prodrugs to the cysteine-34 position of endogenous albumin after IV administration; and (2) release of the albumin-bound drug at the tumor site due to the incorporation of an acid-sensitive or enzymatically cleavable bond between the drug and the carrier.[22,23]

Endogenous albumin is suitable as a drug carrier because it accumulates in solid tumors due to the pathophysiology of tumor tissue. The tumors are characterized by a high metabolic turnover, angiogenesis, hypervasculature, a defective vascular architecture and impaired lymphatic drainage.[24] In addition, the HS-group (thiol) of cysteine-34 of albumin is a unique and accessible functional group of a plasma protein when one considers that free thiol groups are not present in the majority of circulating serum proteins except for albumin. This group is also the most abundant thiol group in human plasma.

The (6-maleimidocaproyl) hydrazone derivative of doxorubicin (DOXO-EMCH; INNO-206) is a prodrug of the anticancer agent in which doxorubicin is derivatized at its C-13 keto-position with a thiol-binding spacer molecule, ie 6-maleimidocaproic acid hydrazide. The thiol-binding spacer binds with the cysteine-34 of human serum albumin (HSA) which is located in a hydrophobic crevice on the surface of the protein that is approximately 10-12 Å deep.[25] The acid-sensitive hydrazone linker allows doxorubicin to be released either extracellularly in the slightly acidic environment often present in tumor tissue or intracellularly in acidic endosomal or lysosomal compartments after cellular uptake of the albumin conjugate by the tumor cell.

INNO-206 is quantitatively and selectively bound to the cysteine-34 position of endogenous albumin within a few minutes. The reaction follows second-order kinetics. INNO-206 was superior to free doxorubicin, the clinical standard, in a murine renal cell carcinoma model (RENCA) and in 2 mammary carcinoma xenograft models in nude mice (MDA-MB 435 and MCF-7) with regard to antitumor efficacy and toxicity. Complete remissions were achieved with INNO-206 in the RENCA and MDA-MB 435 cell lines in contrast to therapy with doxorubicin.[26-28] Subsequent toxicological studies in mice, rats, and dogs demonstrated a 3- to 5-fold increase in the maximum-tolerated dose (MTD), moderate and reversible myelosuppression, no liver toxicity and immunotoxicity, and no new toxicity compared to doxorubicin.[27] In addition, it has recently been shown that INNO-206 is significantly less cardiotoxic in a chronic rat model when compared to doxorubicin at an equitoxic dose.[28]

2.2 Phase 1 Studies of INNO-206

In a phase 1 clinical study of 41 subjects conducted at the Tumor Biology Center (KTB) in Freiburg, Germany, INNO-206 was administered as a 30-minute infusion on Day 1 of a 21-day treatment cycle for a maximum of 6 cycles. Doses were escalated according to a predetermined schedule until the MTD was reached. Subjects continued treatment until disease progression or until unacceptable toxicity occurred or up to a maximum of 6 treatment cycles.

2.2.1 Phase 1 Pharmacokinetic Analysis (KTB)

Total doxorubicin levels were determined in plasma samples collected from 0 to 72 hours and in urine samples collected from 0 to 24 hours after the first dose of study drug. INNO-206 was determined in its albumin-bound form with a high performance liquid chromatographic (HPLC) method and dual mass spectrometry (MS/MS) detection by Bioproof AG (Munich, Germany) under Good Laboratory Practice (GLP) conditions. Doxorubicin could be determined accurately and precisely in the range of 0.0025 µM to 1.003 µM.

Blood and urine samples for pharmacokinetic analyses were obtained from all subjects during the first cycle. The plasma concentrations of total doxorubicin were well quantifiable up to the end of the collection interval of 72.5 hours. Table 1 shows the mean values of select pharmacokinetic parameters for each dose group.

Table 1 Mean Pharmacokinetic Parameters of Total Doxorubicin per Dose Group

INNO-206 Dose (mg/m^2)	Dox. Equiv. Dose (mg/m^2)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (µmol/L)	AUC_{inf} (h·µmol/L)	AUC_{expol} (%)	V_{z_obs} (L/m^2)	Cl_{obs} ($L/h/m^2$)
27	20 (n=4)	24.8	0.4	11.3	200	16.1	4.45	0.1365
50	40 (n=3)	20.8	0.7	21.5	327	7.4	4.77	0.1606
110	80 (n=3)	17.6	0.6	28.4	519	4.9	5.15	0.1998
188	135 (n=6)	18.2	0.5	60.3	1046	7.7	4.57	0.1700
200	150 (n=3)	21.2	0.5	104.9	1602	7.6	3.78	0.1291
240	180 (n=3)	20.2	0.5	96.1	1453	7.6	5.01	0.1716
270	200 (n=6)	25.3	0.5	73.4	1392	15.5	7.28	0.2019
350	260 (n=7)	21.0	0.6	234.6	2554	9.7	4.88	0.1563
460	340 (n=6)	38.2	0.9	145.3	3341	22.3	2.14	0.0432

The mean half-lives ranged between 17.6 hours and 38.2 hours for all 9 treatment groups. There was no clear correlation between the terminal half-lives and the dose of INNO-206 except that the longest terminal half-lives were observed in the group receiving the highest dose. In general, values for C_{max} and AUC_{inf} increased proportionally with the dose, ie, a dose dependency for C_{max} and AUC_{inf} was observed, although the dose groups receiving 200, 270, and 460 mg/m^2 INNO-206 did not fit to the overall trend. No increase of the time at maximum concentration was observed within the dose groups receiving INNO-206 doses of 27 to 270 mg/m^2. Maximum plasma concentrations in dose groups receiving INNO-206 doses of 350 and 460 mg/m^2 were reached later between 0.5 and 2.5 hours after the beginning of the infusion. There was no correlation between clearance and the dose of INNO-206 administered.

2.2.2 Phase 1 Safety Analysis (KTB)

The safety profile of INNO-206 was assessed using adverse event (AE) data (occurrence, intensity, and relationship to study medication), Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiograms (ECGs), echocardiograms (ECHOs), vital signs (blood pressure, respiratory rate, and temperature), hematologic and biochemistry laboratory results, and any neurological and physical examination findings. Adverse events were monitored continuously and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 2.0). For AEs without

CTCAE grades, toxicity was assessed as: 1=mild, 2=moderate, 3=severe, and 4=life-threatening.

Dose-limiting toxicity (DLT) was defined as any of the following drug-related AEs occurring during Cycle 1: grade 2 neurotoxicity; grade ≥3 non-hematological toxicity (excluding alopecia); grade 4 complicated neutropenia (absolute neutrophil count [ANC] <500/µL **and** fever ≥38.5°C or clinical signs of infection); grade 4 neutropenia lasting ≥7 days; or grade ≥3 thrombocytopenia with or without hemorrhagic complications.

All 41 subjects enrolled in the phase I study were included in the safety analysis. The hematologic and non-hematologic toxicities observed are discussed in the following sections.

2.2.2.1 Hematologic Toxicity (KTB)

As shown in Table 2, drug-related mild to moderate (grade 1-2) hematologic toxicity occurred at all dose levels. Subjects treated at 27, 110, and 200 mg/m^2 experienced the mildest toxicities. Grade 3 or 4 toxicity was observed only at the 3 highest doses of 270, 350, and 460 mg/m^2.

Overall, treatment was administered per protocol in the majority of subjects. Twenty subjects (48.8%) received all doses on the prescribed 3-week schedule. Only 13 subjects (31.7%) had dose delays due to prolonged grade 3-4 neutropenia and/or leucopenia during 25 cycles (20.2%). The remaining 8 subjects received only 1 dose (n=7) or had a delay in therapy unrelated to drug toxicity (n=1). The average treatment delay was 1 week (range: 5 – 11 days).

Table 2 Drug-Related Hematologic Toxicities by Dose Level

INNO-206 Dose (mg/m^2)	Doxorubicin Equivalent Dose (mg/m^2)	Anemia N(%)			Leucopenia N(%)			Neutropenia N(%)			Thrombocytopenia N(%)		
		Gr 1-2	Gr 3	Gr 4	Gr 1-2	Gr 3	Gr 4	Gr 1-2	Gr 3	Gr 4	Gr 1-2	Gr 3	Gr 4
27	20 (n=4)	--	--	--	1 (25.0)	--	--	--	--	--	--	--	--
50	40 (n=3)	--	--	--	1 (33.3)	--	--	--	--	--	1 (33.3)	--	--
110	80 (n=3)	1 (33.3)	--	--	--	--	--	--	--	--	--	--	--
188	135 (n=6)	3 (50.0)	--	--	1 (16.7)	--	--	--	--	--	2 (33.3)	--	--
200	150 (n=3)	--	--	--	--	--	--	1 (33.3)	--	--	--	--	--
240	180 (n=3)	1 (33.3)	--	--	--	--	--	--	--	--	1 (33.3)	--	--
270	200 (n=6)	2 (33.3)	--	--	--	2 (33.3)	--	1 (16.7)	--	1 (16.7)	--	--	--
350	260 (n=7)	2 (28.6)	--	--	2 (28.6)	2 (28.6)	1 (14.3)	--	5 (71.4)	1 (14.3)	2 (28.6)	--	--
460	340 (n=6)	5 (83.3)	--	--	1 (16.7)	2 (33.3)	3 (50.0)	--	2 (33.3)	4 (66.7)	--	2 (33.3)	--
	Total	14 (34.1)	0.0	0.0	6 (14.6)	6 (14.6)	4 (9.8)	2 (4.9)	7 (17.1)	6 (14.6)	6 (14.6)	2 (4.9)	0.0

2.2.2.2 Non-hematologic Toxicity (KTB)

Thirty-five subjects (85.4%) experienced at least 1 non-hematologic AE that the Principal Investigator considered at least possibly related to study drug. The majority of AEs were mild or moderate in severity (grade 1–2). The most frequent events (>20% of subjects) were nausea (19 subjects [46.3%]), fatigue (18 subjects [43.9%]), mucositis (13 subjects [31.7%]), and alopecia (9 subjects [22.0%]).

Grade 3 or 4 toxicity was observed primarily at the 3 highest dose levels (270-460 mg/m^2). Grade 3 fatigue was reported by 3 subjects (7.3%) and grade 3 mucositis by 4 subjects (9.8%). Grade 3 stomatitis and grade 3 dysphagia were each reported by 1 subject (2.4%). Two subjects at the 270 mg/m^2 dose level developed grade 3 somnolence, confusion, and depressed level of consciousness (LOC).

Biochemical toxicities were limited to a few isolated changes in clotting factors, serum bilirubin, potassium, and alkaline phosphatase that were not considered to be clinically relevant. Other minor deviations in some biochemical parameters (generally grade 1) were also not regarded to be clinically relevant. A total of 15 subjects (36.6%) experienced elevations in liver enzymes. These changes were observed across all but the 200 mg/m^2 dose group. Some of the subjects with increased enzymes had metastases to the liver.

Extravasation (~20 mg) with tissue swelling and erythema occurred in 1 subject treated with INNO-206 at a dose of 200 mg/m^2. The subject was treated with dimethyl sulfoxide and dexrazoxane beginning 4 hours after the incident. No necrosis occurred and the subject went on to receive further INNO-206 infusions without other clinical sequelae.[14]

No clinical signs of CHF were observed. Pre-treatment and post-treatment ECHO results in 18 subjects showed no significant shortening of the ejection fraction. There were no clinically relevant blood pressure or heart rhythm AEs during the study and none of the subjects had clinical indications of deteriorated left cardiac function through the post-treatment follow-up period.

2.2.2.3 Determination of the Maximum Tolerated Dose

Dose escalation is outlined in Table 3. In summary, there were no DLTs among the three subjects per cohort treated at the first 4 dose levels (27, 50, 110, and 188 mg/m^2). The third subject treated at 270 mg/m^2 experienced grade 3 leucopenia and grade 4 neutropenia; therefore, the cohort was expanded to 6 subjects. No further myelotoxicity was observed; however, 2 of the additional subjects experienced grade 3 drug-related neurological events (somnolence, confusion, and depressed LOC). The study was temporarily stopped at this point and these AEs were discussed with the local Ethics Committee in Freiburg, Germany. It was determined that intercurrent renal dysfunction and sepsis unrelated to the study drug may have contributed to these events. The study was then restarted with 3 additional subjects at the 188 mg/m^2 dose level. Dose escalation continued in smaller increments for safety reasons. Subsequently, there were no DLTs at the 200, 240, and 350 mg/m^2 dose levels. At 460 mg/m^2, leucopenia, neutropenia, and mucositis were dose limiting in the first 3 subjects; therefore, the cohort was expanded to 6 subjects. The 3 additional subjects also experienced dose-limiting mucositis, leucopenia, or neutropenia/neutropenic fever. Thus, the 460 mg/m^2 dose was judged to be the MTD. Based on these results, it was decided to test 350 mg/m^2 in a phase 2 trial. However, in order to gain further experience at the 350 mg/m^2 dose level, that cohort was expanded from 3 to 7 subjects. Two of the 4 additional subjects developed DLTs of neutropenic fever and mucositis.

A more recent phase 1 study is being completed at the Sarcoma Oncology Center in Santa Monica, CA. Three dose levels have been tested (230, 350, and 450 mg/m^2, equal to 165, 260, and 325 mg/m^2 of doxorubicin equivalent). Similar to the initial phase 1 trial, the MTD of INNO-206 is 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent). Dose-limiting toxicities

included grade 4 neutropenia and mucositis. No cardiac toxicities have been observed to date.

Table 3 Dose Escalation and Determination of the MTD

INNO-206 Dose (mg/m^2)	Doxorubicin Equivalent Dose (mg/m^2)	Initial Pts. Enrolled	Add'l Pts. Enrolled	Total Pts. Enrolled in Dose Level	No. Pts. with DLT	MTD Reached?	RP2D Reached?
27	20	3	1[a]	4	0	No	No
50	40	3	0	3	0	No	No
110	80	3	0	3	0	No	No
188	135	3	3	6	0	No	No
270	200	3	3	6	1[b]	No	No
200	150	3	0	3	0	No	No
240	180	3	0	3	0	No	No
350	260	3	4	7	2	No	Yes
460	340	3	3	6	6	Yes	No

[a] Subject 3 had an ileus due to tumor progression during Cycle 1 and was replaced.

[b] Subjects 18 and 19 had grade 3 drug-related somnolence, confusion, and depressed LOC. However, intercurrent illness (renal dysfunction and sepsis, respectively) may also have contributed to these events.

2.2.2.4 Withdrawals, SAEs, and Deaths

Six subjects (14.6%) withdrew from treatment as a result of grade 3 and 4 AEs (Table 4). In four of these subjects, the AEs were drug-related and occurred during Cycle 1. Two subjects at the 270 mg/m^2 dose level withdrew due to possibly related depressed LOC and confusion, although the Principal Investigator and the local Ethics Committee in Freiburg, Germany, considered that the events could also have been caused by intercurrent illness (renal dysfunction and sepsis, respectively).

Table 4 Summary of Withdrawals Due to Adverse Events

Pt. No.	INNO-206 Dose (mg/m^2)	Doxorubicin Equivalent Dose (mg/m^2)	Adverse Event(s)	CTC Grade	Cycle	Study Drug Relationship
4	27	20	Cholecystitis	3	2	Unlikely
18	270	200	Depressed LOC[a], Confusion	3	1	Possible
19	270	200	Depressed LOC[a], Confusion	3	1	Possible
36	460	340	Mucositis	3	2	None
38	350	260	Febrile Neutropenia	4	1	Probable
40	350	260	Mucositis, Neutropenia	3	1	Possible

LOC[a] = level of consciousness

Serious adverse events (SAEs) occurred in 23 subjects (56.1%) across all dose levels with the exception of the 200 mg/m^2 cohort. Serious adverse events with the highest frequency were dyspnea and tumor progression (5 subjects each), pneumonia (3 subjects), and pain, mucositis, neutropenic fever, depressed LOC, and confusion (2 subjects each). The events resolved or improved in the majority of the subjects.

Eight subjects (19.5%) experienced drug-related SAEs. Neutropenic fever, depressed LOC, and confusion were experienced by 2 subjects each. Leucopenia, decreased vision, phlegmonia, neutropenia, peripheral neuropathy, mucositis, and thrombocytopenia were experienced by 1 subject each.

A total of 6 subjects (14.6%) died due to disease progression within 30 days of a dose of INNO-206 (Table 5). Three subjects died while on study and 3 subjects died after they had discontinued. The deaths occurred at the 27, 110, 188, 270, and 460 mg/m^2 dose levels. None of the deaths was attributed to the study drug.

Subject 3 developed an ileus and died 29 days after the first dose of INNO-206. Subjects 9 and 14 died 27 and 21 days, respectively, after their second treatment due to tumor progression. Subject 19 had progression of liver metastases and died 24 days after the first dose. Subject 20 died 17 days after the third dose of study drug due to tumor progression. Subject 37 experienced respiratory insufficiency and died 21 days after the first dose.

Table 5 Summary of Deaths

Pt.No.	INNO-206 Dose (mg/m^2)	Doxorubicin Equivalent Dose (mg/m^2)	No. of Doses	Date of Last Dose	Date of Death	Cause of Death
3	27	20	1	16 Oct 03	14 Nov 03	Disease progression
9	110	80	2	05 Feb 04	03 Mar 04	Disease progression
14	270	200	2	05 May 04	26 May 04	Disease progression
19	270	200	1	14 May 04	07 Jun 04	Disease progression
20	188	135	3	06 Aug 04	23 Aug 04	Disease progression
37	460	340	1	23 Jun 05	14 Jul 05	Disease progression

2.2.3 Phase 1 Efficacy Analysis (KTB)

Tumor response to therapy was assessed with the appropriate scans or examinations after every other cycle, whenever possible, and evaluated using Response Evaluation Criteria in Solid Tumors (RECIST).[29]

All subjects who received at least 2 cycles of therapy without major protocol violations were considered evaluable for response. In addition, subjects who discontinued the study before completing the second cycle because of disease progression were also considered evaluable. Of the 41 treated subjects, 30 (73%) were included in the assessment of response to INNO-206 (Table 6). Reasons subjects were unevaluable included: no post-baseline evaluation performed (n=4), only non-target lesions evaluable (n=4), death due to tumor progression (n=2), and non-evaluable target lesion (n=1).

Table 6 Summary of Tumor Response (n=30)

INNO-206 Dose (mg/m^2)	Doxorubicin Equivalent Dose (mg/m^2)	PR[a]	SD[b]	PD[c]
27	20	–	1	1
50	40	–	1	2
110	80	–	–	2
188	135	–	4	1
200	150	–	3	–
240	180	1	–	1
270	200	–	–	3
350	260	1	3	1
460	340	1	3	1
	Total	**3**	**15**	**12**

PR[a] = partial response
SD[b] = stable disease
PD[c] = progressive disease

All subjects entered the study with evidence of disease progression. There were no complete responses (CR); however, 3 subjects (10%) achieved partial responses (PR). All 3 subjects were anthracycline-naïve; brief summaries of their response to INNO-206 follow. An additional 15 subjects (50%) experienced transient stable disease (SD) ranging from 2 to 15 weeks. Twelve subjects (40%) showed evidence of progression during treatment.

Subject 28 with small cell lung cancer pretreated with etoposide and cisplatin progressed following therapy and developed pleural effusions and clinical deterioration (dyspnea and cough) prior to study entry. The subject received 6 cycles of INNO-206 at a dose of 240 mg/m². Disease progression was documented by computed tomography (CT) scan 14 months after discontinuation of study drug. Good tumor control was achieved and the time to progression was approximately 19 months (82.6 weeks).

Subject 29 with liposarcoma pretreated with an angiogenesis inhibitor received INNO-206 at a dose of 350 mg/m^2. The subject achieved a PR with a time to progression of 17 weeks.

Subject 33 with metastatic breast cancer was pretreated with adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), various hormonal treatments (trenantone, letrozole, exemestan, and tamoxifen), and trofosfamide. She received INNO-206 at a dose of 460 mg/m^2 and had a PR and time to progression of 24 weeks.

2.3 Study and Dose Rationale

Despite advances in the management of cancer with radiotherapy, chemotherapy, and surgery, many solid tumors remain incurable, especially when the tumor has metastasized or is bulky at presentation. There is an urgent need for treatments with new mechanisms of action and improved side effect profiles, particularly those effective against bulky disease and those with potential for synergism in combination with chemotherapy or radiotherapy.

INNO-206 is an albumin-binding prodrug of the anticancer agent doxorubicin. Doxorubicin, the active ingredient of INNO-206, is classed as an antitumor antibiotic. Several modes of action for doxorubicin have been postulated including intercalation of DNA, inhibition of topoisomerase II, induction of apoptosis, inhibition of RNA synthesis, and/or interaction with the cell membrane.[15-17]

Doxorubicin is a widely used antineoplastic agent in the treatment of leukemia and lymphoma, breast and ovarian carcinoma, as well as in many other solid tumors.[17,18] The

clinical application of this anthracycline drug is, however, limited by its toxic dose-related side effects, such as myelosuppression, gastrointestinal disorders, stomatitis, cumulative cardiotoxicity, and extravasation.[18,19,20]

In order to circumvent these limitations and to improve the therapeutic potential of anticancer drugs, INNO-206 was developed. With INNO-206, due to a high metabolic turnover of tumor tissue and the enhanced vascular permeability of the blood vessels of malignant tissue for circulating macromolecules, the plasma protein albumin preferentially accumulates in solid tumors.[26] Once within the relatively acidic environment of the tumor, the acid-sensitive linker is cleaved allowing the release of free doxorubicin.

The dose for this phase 2b study will be 350 mg/m^2 of INNO-206 (doxorubicin equivalent dose of 260 mg/m^2) administered over 30 minutes via intravenous infusion (IVI) once every 3 weeks for a maximum of 6 cycles. The dose level is 1 dose level below the MTD established in 2 phase 1 trials and was chosen with the aim of improving the side effect profile of the drug while still administering a much higher dose than standard tolerated doxorubicin (60-75 mg/m^2 per cycle, 6 cycles total). A 3-week administration schedule has demonstrated clinical benefit in the previous human study and provides a convenient clinical regimen of INNO-206 administration, both as monotherapy and in combination with commonly used chemotherapeutic agents. The dose of doxorubicin is 75 mg/m^2, which is the standard dose used to treat advanced soft tissue sarcoma. It will also be administered over 30 minutes via IVI once every 3 weeks for a maximum of 6 cycles.

The sponsor believes that the proposed study is acceptable in the context of its benefit/risk ratio.

3. OBJECTIVES

3.1 Primary Objectives

1) The primary objective of this study is to determine the preliminary efficacy of administration of INNO-206 compared to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by progression-free survival, progression-free survival at 4 and 6 months, tumor response, and overall survival.

3.2. Secondary Objectives

1) The secondary objective of this study is to evaluate the safety of INNO-206 compared to doxorubicin in this population as assessed by the frequency and severity of AEs, abnormal findings on physical examination, laboratory tests, vital signs, MUGA/cardiac ultrasound evaluations, ECG results, and weight.

4. INVESTIGATIONAL PLAN

4.1 Overview

This is a phase 2b, randomized, open-label, prospective, multicenter study comparing treatment with INNO-206 to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have not been previously treated with any chemotherapy except potentially as adjuvant or neoadjuvant chemotherapy, (including ≤ 3 cycles or ≤225 mg/m^2 doxorubicin or Doxil®) and no evidence of tumor recurrence has occurred for at least 12 months. One hundred five (105) subjects will be enrolled and randomized 2:1 to receive either INNO-206 or doxorubicin. INNO-206 at a dosage of 350 mg/m^2 (doxorubicin equivalents of 260 mg/m^2) will be administered as a 30 minute IVI on Day 1 of each cycle to approximately 70 subjects. Doxorubicin (75 mg/m^2) will be administered to approximately 35 subjects per the instructions outlined in the package insert (Study Reference Manual) on Day 1 of each cycle. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be monitored every 15 min starting immediately prior to either INNO-206 or doxorubicin dosing and ending approximately 30 min after the completion of the infusion.

An individual cycle of therapy will be defined as a 3-week (21-day) period. Cycles will be repeated every 3 weeks. Multiple cycles may be administered until the subject is withdrawn from therapy (see Section 5.4) or until a maximum of 6 cycles are administered. After 6 cycles of therapy, additional cycles may only be administered following consultation with the CytRx Medical Monitor.

Overall response rates as well as individual categories of response (CR, PR, SD, and PD) will be determined using RECIST 1.1.[28] Time-to-event endpoints, including PFS and OS will be assessed using the Kaplan-Meier method.[30] Evaluation of 4- and 6-month progression-free survival will also be performed. Toxicity (adverse events) will be recorded using the NCI CTCAE, version 4.0 (published 28 May 2009) (see Appendix C).

4.2 Primary Endpoint

1) To evaluate the progression-free survival in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas.

4.3 Secondary Endpoints

1) To evaluate the overall survival, progression-free survival at 4 and 6 months, and objective overall response rate (ORR; RECIST 1.1 criteria, Study Reference Manual) in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas.
2) To evaluate the treatment-related toxicities in this subject population.

5. STUDY POPULATION

5.1 Subject Selection and Study Duration

One hundred and five (105) subjects will be recruited from approximately 30 study centers in the United States, Hungary, Romania, Ukraine, Russia, India and Australia. Up to 32 subjects may be enrolled in India, with the remaining subjects distributed in other locations. The expected duration of this study is 27 months. Enrollment into the screening or treatment phase of the study will be stopped when the anticipated or actual subject numbers have been achieved across all study sites.

5.2 Inclusion Criteria

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

1. Age between 15-80 years (US only), and 18-80 (ROW), 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 of intermediate or high grade.
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. 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 that ensures the subject will be able to keep all study-related appointments.

5.3 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 either doxorubicin or Doxil®
3. Palliative surgery and/or radiation treatment less than 4 weeks prior to Randomization.
4. Exposure to any investigational agent within 30 days of Randomization.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, GIST, dermatofibrosarcoma, Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas and unresecatble low grade liposarcomas.

7. Central nervous system metastasis.
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 >1.5×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, coagulation tests (PT, PTT, INR) >1.5×ULN, and albumin <2.0 g/dL.
10. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.
11. Current serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
13. History or signs of active coronary artery disease with or without angina pectoris.
14. Serious myocardial dysfunction defined 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 3 weeks prior to 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.

5.4 Subject Enrollment

This is an open-label, randomized study. Subject ID number will be assigned by the site at the time the subject signs an Informed Consent Form (ICF). Subjects will be randomized through the IXRS system at least five days prior to the planned Cycle 1-Day 1 visit in a 2:1 ratio (INNO-206:doxorubicin) across all study sites. A copy of the signed informed consent will be required for study entry.

The exact date and time of each administration of study medications will be recorded in the electronic case report form (eCRF). INNO-206 or doxorubicin will be administered according to the clinical study protocol only to subjects who have given written informed consent. Subjects withdrawn from the study will retain their subject ID number. New subjects must always be allotted a new subject ID number.

5.5 Subject Discontinuation

Subjects will be discontinued from the treatment under the following circumstances:

1) Disease progression.

2) Subject's physician considers a change of therapy would be in the best interest of the subject.
3) Subject requests discontinuation.
4) Continued unacceptable toxicities despite optimal treatment or dose reduction.
5) Subject becomes pregnant or fails to use adequate birth control (for those subjects who are fertile).
6) Need for any treatment not allowed by the protocol.
7) Non-compliance.

5.6 Study Discontinuation

CytRx has the right to terminate the participation of either an individual site or the study at any time. Reasons for terminating the study include, but are not limited to, the following:

1) Incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
2) Subject enrollment is unsatisfactory.
3) Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

6. STUDY TREATMENT

6.1 Formulation and Storage

INNO-206 will be supplied as a lyophilized powder by Lyophilization Technology (Ivyland, PA) or Baxter Oncology GmbH (Germany). The powder will be supplied in 50-mL clear glass vials with siliconized Teflon stoppers containing 200 mg INNO-206. Vials will be stored at –20°C and protected from light. Additional light protection during the short-term infusion is not necessary.

The packaging, labeling, and distribution of INNO-206 will be performed by Almac (United Kingdom or United States), according to all applicable legal requirements. All drug supplies must be stored in accordance with the instructions from CytRx. Until dispensed to the subjects, the study medication will be stored in a securely locked area, accessible to authorized personnel only. Instructions for ordering drug will be specified in the Study Reference Manual.

Doxorubicin HCL (packaged, labeled and distributed by Almac (United Kingdom or US) for IV use is supplied as a sterile red-orange parenteral containing 0.9% NaCl and water for injection. The vials must be stored refrigerated (2-8^{o}C), protected from light. Refer to the package insert in the Study Reference Manual for complete information.

6.2 INNO-206 and Doxorubicin Administration

Treatment must be administered in a hospital, clinic or other out-patient setting appropriate for chemotherapeutic infusions. No investigational or commercial agents or therapies other than those described in Section 6.6 may be administered with the intent to treat the subject's malignancy.

The solution for infusion will be prepared at each investigational site by trained personnel. Detailed guidelines for the preparation and administration of INNO-206 are provided in the Study Reference Manual. INNO-206 will be administered by IVI over a period of approximately 30 minutes into a peripheral line (or central line, if available) once every 3 weeks for a maximum of 6 cycles. INNO-206 infusion should be completed within 2 hours after reconstitution and dilution into Lactated Ringer's solution.

Preparation and administration of doxorubicin should follow the instructions outlined in the package insert (see the Study Reference Manual).

Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be monitored every 15 minutes starting immediately prior to the INNO-206 or doxorubicin infusion and ending approximately 30 minutes after completion of the infusion.

In the event of extravasation during the infusion of either INNO-206 or doxorubicin, the injection should be immediately terminated and subjects treated according to local site protocols. Treatment may include the intermittent application of ice to the site for 15 minutes q.i.d. for a few days (see Appendix H for additional information). The infusion should then be restarted in another vein.

WARNING: INNO-206 is reconstituted in a 50% water:ethanol mixture; thus, between 50-100 mL of 50% ethanol will be administered over a 30 minute period. Please use precaution in administration of concomitant medications that may interact with acute ethanol exposure. Monitor the subject closely for signs of ethanol intoxication prior to releasing the subject from the study site. See Appendix I for a list of concomitant medications that should be avoided. It is <u>required</u> that subjects have a designated driver on days they receive INNO-206 treatment.

6.3 Body Surface Area Calculation

The calculation of the dose of INNO-206 or doxorubicin will be based on the subject's body surface area (BSA) using the Du Bois & Du Bois formula (www.halls.md/body-surface-area/bsa.htm). The BSA will be calculated at Cycle 1-Day 1 and before each cycle, if there has been a >10% weight change from Cycle 1-Day 1. If the BSA is recalculated, the dose will be adjusted downward to the nearest whole milligram. Instructions for determining the subject's BSA will be provided in the Study Reference Manual.

6.4 Dose Modification for Toxicity

Toxicities will be graded using the NCI CTCAE v4.0 (see Appendix C). If toxicity occurs during or after any treatment cycle, the toxicity will be graded and appropriate supportive care treatment may be administered to decrease the signs and symptoms (eg, antiemetics, antidiarrheals, antipyretics, antihistamines).

Doses may be reduced in individual subjects in accord with the schedule in Table 7 for each dose level of INNO-206. Doses that have been reduced for toxicity will not be escalated back to the starting level. A subject may not have more than 3 dose reductions. Growth factors may be used to treat hematologic toxicity and will not constitute a dose reduction.

Dose reductions for doxorubicin should follow the instructions outlined in the package insert (see Study Reference Manual and Table 7).

A maximum of a 3-week treatment delay is permitted to allow recovery of toxicities. If a treatment delay greater than 3 weeks is required for recovery of toxicities, or any subject experiences recurring toxicities despite 3 dose reductions, the subject will be removed from the treatment period of the study.

Table 7 Dose Reduction Schedule for INNO-206 and Doxorubicin

Dose Level	INNO-206 Dose (mg/m^2)
Level 0 (baseline)	350→270
Level -1	270→200
Level -2	200→150

Plasma Bilirubin Concentration (mg/dL)	Doxorubicin Dosage Reduction
1.2-3	50% (75 → 37.5 mg/m^2)
3.1-5	75% (75 → 18.75 mg/m^2)

6.4.1 Non-hematological Toxicity

Dose reductions for non-hematologic toxicity that occur despite adequate background medical therapy should be undertaken in accordance with Table 8.

Table 8 Dose Reduction for Non-hematologic Toxicities

Adverse Event Grade	Action
Grade ≤2	Maintain dose level
Grade 3	Dose reduction by one level **OR** review with Medical Monitor
Grade 4	Review with Medical Monitor to determine if the subject can continue in the study with an appropriate dose adjustment.

Subjects who develop ≥ grade 3 heart failure should be permanently discontinued. For subjects who develop < grade 3 heart failure or left ventricular systolic dysfunction, treatment with INNO-206 or doxorubicin should be suspended and optimal medical treatment implemented to manage the heart failure. If the left ventricular ejection fraction improves to ≥50% with optimal treatment within 1 month, INNO-206 or doxorubicin can be restarted at the original dose level. Following the reintroduction of either drug, if the subject develops symptoms of ≥ grade 2 heart failure or grade 3 left ventricular systolic dysfunction, treatment with either INNO-206 or doxorubicin should be permanently discontinued.

For subjects who develop grade 4 left ventricular systolic dysfunction at any time, INNO-206 or doxorubicin therapy should be permanently discontinued.

6.4.2 Hematologic Toxicity

Investigators should attempt to manage hematologic toxicities with the use of growth factors and supportive measures. For grade 3-4 hematologic toxicity, the next cycle should not be started until recovery to grade ≤1. However, a reduction by 1 dose level is mandatory for the next cycle in subjects who experience grade 4 toxicity that does not recover to ≤ grade 1 prior to the subsequent scheduled chemotherapy cycle.

6.5 Intended Dose Delays

Intended cycles may be delayed for non-toxicity reasons for up to 5 days (for reasons such as scheduling conflicts), but only with prior documented approval of the Medical Monitor.

6.6 Concomitant Therapy

Necessary supportive measures for optimal medical care may be given throughout the study, including IV antibiotics to treat infections, blood components, and anti-emetics. Additional care will be administered as indicated by the treating physician and the subject's medical need. No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study. All concomitant medications and supportive therapy must be recorded on the appropriate eCRF.

Concomitant use of medications associated with a high incidence of QT prolongation are not allowed (Appendix G) during study treatment.

Localized radiotherapy for the treatment of symptomatic lesions is permitted following approval from the CytRx Medical Monitor. INNO-206 or doxorubicin administration should not be withheld during this type of therapy. If localized therapy such as radiation therapy is necessary, those lesions should not be included in RECIST evaluations. If skin toxicity occurs, the subject should be removed from study. For more extensive radiotherapy, such as chest or abdominal field radiation, treatment with INNO-206 or doxorubicin should be withheld during therapy for a maximum of 4 weeks.

Routine **prophylactic use** of a colony-stimulating factor (G-CSF or GM-CSF) should be used according to the American Society of Clinical Oncology guidelines[31] (Appendix E).

Erythropoietin is permitted if clinically indicated.

6.7 Concomitant Therapies Requiring Caution

Doxorubicin may potentiate the toxicity of other antineoplastic agents.

- Concomitant administration with calcium-channel blocking agents may potentiate doxorubicin-induced cardiotoxicity;
- Concomitant administration with cyclosporine may induce seizures and/or coma;

- Concomitant administration with live vaccines to immunosuppressed subjects, including those undergoing cytotoxic chemotherapy, may be hazardous. Phenobarbital may increase the elimination of doxorubicin; streptozocin may inhibit hepatic metabolism of doxorubicin; doxorubicin may decrease serum levels of phenytoin.

Because INNO-206 is a doxorubicin prodrug, these interactions may also be applicable.

7. STUDY ASSESSMENTS

7.1 Laboratory Assessments

All hematology, blood chemistries, urinalyses, and serum or urine pregnancy tests (if applicable) will be performed by the local or central laboratory (ie, in those countries where applicable) for each investigational site.

Prior to study enrollment, each subject will have the following assessments (see Appendix A):

7.1.1 Within 21 Days Prior to First Dose

1) Written informed consent and Medical history including concurrent baseline conditions (using NCI CTCAE version 4.0; Appendix C), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
2) Complete physical examination including height (cm) and weight (kg).
3) ECOG Performance Status (ECOG PS) (see Appendix B).
4) Vital signs (blood pressure, pulse, respiratory rate, and temperature).
5) Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated).
    a. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary if the scans were performed as qualified by CoreLab.
    b. In addition to the CT / MRI scan, tumor size may also be assessed utilizing visual or palpable lesions on physical examination including full assessment of all known metastases (see RECIST 1.1 criteria[29] in Section 8.2).
    c. A brain scan is required to exclude brain metastasis if clinically indicated.
6) Electrocardiogram (ECG).
7) Echocardiogram (ECHO) (ejection fraction must be recorded) or MUGA.
8) Complete blood count (CBC) with differential and platelet count.
9) Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, lactate dehydrogenase (LDH), creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
10) Coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], and International Normalized Ratio [INR]).
11) Urinalysis (lab): protein, specific gravity, glucose, and blood.
12) Serum troponin.
13) Serum or lab urine pregnancy test (if applicable).
14) Concomitant medication notation (to include all medications taken within 30 days prior to study enrollment).

7.2 On-Study Assessments

Subjects must begin Cycle 1 within 21 days of signing the informed consent document and after the screening assessment. Treatment will be administered by qualified and trained site

personnel in a hospital, clinic, or other out-subject setting appropriate for chemotherapeutic infusions. All assessments must be performed within 72 hours of each specified time parameter, with the exception of Cycle 1 in which assessments must be conducted on the same day (except those noted).

NOTE: Randomization of subject must be done through the IXRS system at least 5 days prior to the planned Cycle 1-Day 1 visit.

7.2.1 Day 1 of Each Cycle (except where noted)

1) Inclusion/exclusion review (Cycle 1 only).
2) Directed physical exam.
3) Measurement of height (cm) (Cycle 1 only/ if not done as part of screening procedures), weight (kg) and BSA calculation prior to dosing (Cycle 1 only, unless there is a >10% change in bodyweight).
4) ECOG PS (see Appendix B).
5) MUGA or cardiac ultrasound (At the end of Cycles 2, 4, and 6 only)
6) Vital signs (see Section 7.1.2) will be monitored every 15 min starting immediately prior to INNO-206 or doxorubicin dosing and ending approximately 30 min after the completion of the infusion.
7) Hematology: CBC with differential and platelet count (no need to repeat if performed within 21 days of Cycle 1-Day 1 visit).
8) Serum chemistries (see section 7.1.1) (no need to repeat if performed within 21 days of Cycle 1-Day 1 visit).
9) Blood alcohol level within 15 minutes post-infusion for those subjects receiving INNO-206.
10) ECG.
11) Serum troponin (no need to repeat if performed within 21 days of Cycle 1-Day 1 visit).
12) INNO-206 or doxorubicin administration by IVI through a peripheral line (or central line, if available) (see Study Reference Manual). If a burning sensation occurs, see Study Reference Manual for recommendations.
13) Concomitant medication notation.
14) AEs using the NCI CTCAE (see Appendix C).

7.2.2 Tumor Response will be monitored every 6 weeks from Cycle 1-Day 1 during treatment, at end of treatment, 2 months following the End of Treatment scan (for those subjects completing 6 cycles), then every 3 months to disease progression

1) Tumor assessment.
    a. Reassessment of the extent of tumor should be made by the same assessment methods used to establish baseline tumor measurements.
    b. In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.
    c. . For those subjects that leave the study prior to completing Cycle 6, and who do not start another therapy, they can be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. However, if a

subject receives another therapy, they should only be followed for overall survival [OS].

7.2.3 End of Treatment

When the subject completes all 6 cycles of study medication, or withdraws from treatment prior to completing all 6 cycles for any reason, the following assessments will be performed within 21-28 days after completing their last dose of study medication.

1) Directed physical exam, if deemed necessary.
2) ECOG PS (see Appendix B).
3) Vital signs (see Section 7.1.1).
4) Hematology: CBC with differential and platelet count.
5) Serum chemistries (see Section 7.1.1).
6) Urinalysis (see Section 7.1.1).
7) Concomitant medication notation.
8) AEs using the NCI CTCAE (see Appendix C).
9) CT/MRI scan to evaluate disease status (using same imaging method as Screening), if not done within last 14 days. See section 7.2.2
10) ECG, if not done within last 14 days.
11) MUGA or cardiac ultrasound.
12) Serum troponin, if not done within last 7 days.

7.2.4 To be completed 2 months following the End of Treatment scan, then every 3 months to disease progression

1) Directed physical exam.
2) Vital signs (see Section 7.1.1).
3) ECG.
4) CT/MRI scan to evaluate disease status (see section 7.2.2).
5) MUGA or cardiac ultrasound.
6) Hematology: CBC with differential and platelet count.
7) Serum troponin.

7.3 Follow-Up Assessments

Follow-up assessments by telephone will be conducted for all subjects every 8 weeks from the time a subject either withdraws from treatment or at disease progression until the subject is either lost to follow-up, passes away, or the Sponsor stops the study.

7.4 Statistical Considerations

This is a phase 2b, randomized, open-label, multicenter study of INNO-206 or doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have not received chemotherapy or have only received adjuvant or neoadjuvant chemotherapy and have not experienced disease relapse in at least 12 months. The primary endpoint of this study is to compare the progression-free survival between the two treatment arms in this cancer population. Secondary endpoints include determination of overall survival, progression-free survival at 6 months, objective response rates and the frequency of treatment-related toxicities.

One hundred five (105) subjects will be enrolled into this study in the U.S., Hungary, Romania, Ukraine, Russia, India, and Australia.

7.5 Sample Size

Power calculations and subject numbers were calculated based on the progression-free survival (PFS) endpoint. Historical data have shown that the PFS in this population treated with doxorubicin chemotherapy is approximately 4.4 months. Based on the use of a two-sided test at the alpha=0.05 level of significance, a total of 89 progressions will be required for at least 83% power to detect a PFS duration for INNO-206 of 8.5 months. Assuming an 15 month accrual period and 12-month follow-up, further if the dropout rate for INNO-206 treatment group and doxorubicin are 20% each at the end of study (Month 27) respectively and also dropouts follow the exponential distribution, 70 subjects in the INNO-206 treatment group and 35 subjects in the doxorubicin group will be needed to achieve the total of 89 progressions. Therefore, a total of 105 subjects are required according to a randomization ratio of 2:1 (INNO-206:doxorubicin).

7.6 Treatment Assignment and Blinding

This is a phase 2b, randomized open-label trial, with the identity of the treatment known to the subjects, Investigators, and Sponsor. It is planned that subjects enrolled will be treated with INNO-206 or doxorubicin according to the administration schedule described in Section 6.2. Subjects in each group will be stratified according to their initial Performance Status (ECOG 0-1 vs 2) and whether they had received either prior adjuvant or neoadjuvant chemotherapy or no prior chemotherapy.

7.7 Subject Disposition

A detailed description of subject disposition will include:

- A summary of data on subject discontinuation from treatment.
- A summary of data on overall qualification status of all subjects.
- An account of all identified protocol deviations.

All subjects enrolled in the study will be included in the summation. The number of subjects who do not qualify for analysis, who die or discontinue before treatment begins, will be specified.

7.8 Subject Characteristics

Subject characteristics will include a summary of the following:

- Subject demographics.
- Baseline disease characteristics.
- Pre-existing conditions.
- Prior therapies.
- Concomitant medications and treatments.

Other subject characteristics will be summarized as appropriate.

7.9 Efficacy Analysis

The efficacy analysis will include the following parameters: objective response rate (CR + PR), progression-free survival (PFS), progression-free survival at 4 and 6 months, stable disease rate (SD), and overall survival (OS). The efficacy analysis will only be conducted on

subjects who have received at least one dose of study drug and have at least one post baseline tumor assessment.

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.

Progression-free survival is defined as the interval from the date of registration (ie, assignment of subject number) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. Progression-free survival at 4- and 6- months will be estimated by the percentage of subjects achieving these criteria.

Overall survival will be measured from the date of registration (ie, assignment of subject number) to the date of death due to any cause, or the date of last contact (censored observations).

7.10 Interim Analysis

An interim analysis will be performed when 50% of subjects have completed at least 4 cycles of study drug. The overall response rate will be compared between INNO-206 and doxorubicin. Because the interim analysis will not incorporate the possibility of stopping the trial early based on increased efficacy of either arm, and because the primary endpoint will not be analyzed, the type I error rate will not be adjusted.

The interim analysis results may be used to terminate the trial for futility based on the following criterion. Let p_1 and p_2 denote the observed overall response rates in the INNO-206 and doxorubicin arms and let $d=p_1-p_2$ denote the observed difference in response rates. If d is less than 0.03 (for example, if the observed response rates are 0.15 for doxorubicin and 0.17 for INNO-206), then the study will be terminated for futility.

Based on the use of this criterion and an interim analysis sample size of 54 subjects (18 in the doxorubicin arm and 36 in the INNO-206 arm), the study will be terminated either when the upper limit of the two-sided approximate 80% confidence interval for the difference in proportions is approximately equal to 0.17 or less, or when the difference d is less than 0.03. If either criterion is met, the study will be terminated. Only a summary table of the overall response rate will be provided to the study team.

7.11 Safety Analysis

All subjects who receive any amount of INNO-206 or doxorubicin will be included in the safety analyses, which will include the following:

(1) The incidence, severity, duration, causality, seriousness, and type of AEs and changes in the subject's physical examination, vital signs, and clinical laboratory results.

(2) In addition, deaths and other SAEs will be tabulated.

7.12 Progression-free Survival Analyses: Primary Endpoint

Power calculations and subject numbers were calculated based on the progression-free survival endpoint. Historical data have shown that the progression-free survival (PFS) in this population treated with doxorubicin chemotherapy is approximately 4.4 months. Based on the use of a two-sided test at the alpha=0.05 level of significance, and assuming an 15

month accrual period and 12-month follow up, with a 2:1 randomization (70 subjects for INNO-206: 35 subjects for doxorubicin), there would be 83% power to detect a PFS duration for INNO-206 of 8.5 months, based on 89 events.

7.13 Replacement of Subjects

Subjects who are enrolled into the study, but fail to receive INNO-206 or doxorubicin, may be replaced.

7.14 Subject Compliance

INNO-206 or doxorubicin will be administered via IVI by qualified and trained site personnel in a hospital, clinic or other out-subject setting appropriate for chemotherapeutic infusions.

7.15 Quality Assurance

The study will be initiated and conducted under the sponsorship of CytRx Corporation. Study drug, clinical supplies, and eCRFs will be supplied by CytRx or its representative. Representatives of CytRx will monitor the study to verify study data, medical records, and eCRFs in accordance with current ICH GCP guidelines as well as other applicable regulations and guidelines.

7.16 Study Administration

The names, titles, and addresses of the Investigators and study personnel who administer the study medication will be listed in the Site Contacts list for Protocol INNO-206-P2-STS-01 and will be available from CytRx or its representative.

8. EFFICACY

Subjects will be evaluated for response every 6 weeks from Cycle 1-Day 1 during treatment, at End of Treatment, 2 months following the End of Treatment scan (for those subjects completing 6 cycles), and then every 3 months, or if clinical signs are suggestive of progressive disease. For those subjects that leave the study prior to completing Cycle 6, and who do not start another therapy, they can be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. However, if a subject receives another therapy, they should only be followed for overall survival. Tumor measurements and overall response will be recorded in the eCRF. Subjects with PD will be taken off protocol treatment; however, the subject will be encouraged to remain in treatment-free follow-up if medically warranted.

8.1 Response Definitions

8.1.1 Best Overall Response

Best overall response is defined as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for tumor progression, the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

8.1.2 Overall Tumor Response

The overall tumor response rate is defined as the total proportion of subjects who have an objective tumor response (CR + PR). Rates for the individual categories of response (CR, PR, SD, and PD) will also be determined.

8.1.3 Not Evaluable

Subjects will be defined as being not evaluable for response if a radiological assessment cannot be made. These subjects will be counted as treatment failures in the analysis of tumor response data.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy before confirming the CR status.

8.1.4 Progression-free Survival

Progression-free survival (PFS) is defined as the time from enrollment (ie, assignment of subject ID number) to first documentation of objective tumor progression or to death due to any cause in the absence of previous documentation of objective tumor progression. PFS will be censored at the last date the subject was known to be progression-free in subjects who do not have objective tumor progression and who are: 1) still on study at the time of an analysis; 2) are given anti-tumor treatment other than the study treatment; or 3) are removed from study follow-up prior to documentation of objective tumor progression.

8.1.5 Survival

Survival is defined as the time from enrollment (ie, assignment of subject ID number) to date of death. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive.

8.1.6 Analysis Plan

Continuous variables will be summarized using the mean (SD) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of subject characteristics on response and toxicity rates. The distribution of time-to-event endpoints (eg, response duration, progression-free survival, overall survival) will be estimated using the Kaplan and Meier method.[30] Comparison of time-to-event endpoints by important subgroups of subjects will be made using the log-rank test. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

A detailed description of all planned statistical analyses will be presented in the Statistical Analysis Plan.

8.2 Guidelines for Measuring Disease

Antitumor activity will be evaluated by RECIST 1.1 criteria.[29] These response criteria are widely recognized and accepted as the standard criteria for determining response in subjects with solid tumors.

8.2.1 Disease Definitions

Measurable disease is defined as the presence of ≥1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

At Baseline, tumor lesions will be categorized as:

Measurable Lesions: lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant lymph nodes: to be considered pathologically enlarged and measureable, a lymph node must be ≥15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and follow-up, only the *short* axis will be measured and followed.

or

Non-measurable Lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

For special considerations regarding lesion measurability for bone lesions, cystic lesions and lesions with prior local treatment, consult the RECIST 1.1 guidelines in the Study Reference Manual.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before beginning of treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, either a CT scan or documentation including ruler measurements to estimate the size of the lesion, is to be done.

8.2.2 Methods of Measurement

Tumor measurements should be performed using the same method as well as the same staff member per subject, if possible, throughout the study. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of ≤5 mm in slice thickness contiguously. This applies to tumors of the chest, abdomen, and pelvis.

- As a rule, the minimum size of the lesion should be no less than double the slice thickness.

Ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is necessary.

Tumor markers *alone* cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors) if required by protocol.

8.2.3 Baseline Documentation of "Target" and "Non-target" Lesions

Target Lesions: all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs will be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter [LD]), be representative of all involved organs, and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum of the LD will be used as reference to further characterize the objective tumor response.

Non-target Lesions: all other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and will also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

8.2.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm).

Partial Response (PR): ≥30% decrease in the sum of the LD of target lesions, from the baseline sum LD.

Progressive Disease (PD): ≥20% increase in the sum of the LD of target lesions from the smallest sum of the LD recorded since the treatment started; the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of ≥1 new lesion is also considered progression.

Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-target Lesions

Complete Response (CR): disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: persistence of ≥1 non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): appearance of ≥1 new lesion and/or unequivocal progression of existing non-target lesions*.

*Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the independent radiologist should prevail and the progression status should be confirmed later on by the Drug Safety Monitoring Committee (DSMC).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Imaging Manual).

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be classified as having "symptomatic deterioration." Every effort will be made to document the objective evidence of disease progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

8.2.5 Confirmation

Confirmation of a CR, PR, and PD is not necessary for this study.

8.2.6 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

8.2.7 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- For the purposes of this trial, the minimal time interval required between 2 measurements for determination of SD is 6 weeks (at least 2 consecutive assessments 6 weeks apart revealing SD). This time interval takes into account the expected clinical benefit that such a status may bring to the population under study.

9. SAFETY

The investigator is responsible for monitoring the safety of subjects who have enrolled in the study. All adverse events (AEs) occurring after any administration of the study medication will be followed until the event resolves, until the subject begins alternative treatment, or until 30 days after the last dose of study medication. Investigators will grade AEs using the NCI CTCAE, version 4.0 (published 28 May 2009) (see Appendix C).

Investigators are required to document all AEs occurring during the clinical trial, commencing with the first dose of study medication and including the protocol-defined post-treatment follow-up period (21 CFR §312.64[b]) on designated eCRF pages. AEs occurring following the signature of the informed consent, but prior to the first dose of study medication will not be reported as AEs. It is also important to record all AEs that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Serious adverse events (SAEs), as defined below, must be reported to CytRx or its representative within 24 hours of knowledge of their occurrence.

9.1 Adverse Events

An AE is any unfavorable medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the eCRF. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE.

A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for SAEs.

Subjects should be instructed to report any event that they experience to the Investigator starting from the time they sign the Informed Consent Document. Investigators should assess AEs at each visit.

AEs occurring prior to study drug infusion should be recorded on the Medical History page of the eCRF. AEs during the clinical trial, starting at the time of the initial study drug infusion, and the follow-up period should be recorded on the appropriate AE page of the eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF.

9.2 Serious Adverse Events (21 CFR §312.32)

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
  - Life-threatening is defined as an event with immediate risk of death from the event as it occurred. It does not include an event that might have caused death if it occurred with a greater severity.
- In-patient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other listed outcomes above.

9.3 Adverse Event Severity

AE will be graded according to the NCI CTCAE, Version 4.0 (see appendix C)

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on subject/event outcome at the time of the event. For example, the NCI CTCAE grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

9.4 Causality Assessment

The relationship of an AE to the study drug must be classified as one of the following:

- **Unrelated:** The AE is clearly not related to the study medication
- **Possibly Related:** The AE may be related to the study medication
- **Definitely Related:** The AE is clearly related to the study medication

9.5 Reporting Serious Adverse Events

All SAEs occurring during the course of the study or within 30 days of the last administration of study medication must be reported to CytRx or its representative **within 24 hours** of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). The SAE reporting period ends if the subject begins an alternative therapy or 30 days after the last administration of study drug. Reporting is done by faxing a completed SAE Report Form or by direct telephone communication. When the initial report is made verbally or by telephone, a written confirmation **within a further**

24 hours must follow. Clinical safety personnel are available for SAE reporting on a 24-hour basis. Reports are reviewed during normal business hours.

Safety and Emergency Contact Information:

Toll-Free Hotline: 1-877-462-0134

Toll-Free Fax: 1-877-464-7787

The investigator will be requested to supply detailed information regarding the event. All serious and unexpected AEs/SAEs must also be reported to the reviewing IRB and a copy of that report must be retained at the investigative site and filed in the Trial Master File.

9.6 SAE Follow-Up

For all SAEs occurring after first dose of study medication or within 30 days of the last administration of study medication, the investigator must submit follow-up reports to CytRx or its representative regarding the status of the SAE and the subject's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the subject receives alternative therapy, or the subject dies.

9.7 Pregnancy

While not considered a SAE unless a serious criterion is met, pregnancies occurring in subjects enrolled on the study or in their partners must be reported. The investigator should complete the pregnancy report form and fax it to INC Research Global Drug Safety (toll-free fax number 1-877-464-7787) within 24 hours of knowledge of the pregnancy.

10. INVESTIGATOR REQUIREMENTS

10.1 Protocol Adherence

Each investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by CytRx prior to seeking approval from the IRB/EC. Each investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria.

10.2 Electronic Case Report Form (eCRF) Completion

This study is using an electronic data capturing system (EDC). All electronic case report forms (eCRFs) are to be filled out completely by examining personnel or the study/data coordinator within 5 days of the completion of a subject's visit.

10.3 Monitoring Requirements

This study will be monitored by an authorized CytRx representative in accordance with current ICH GCP guidelines and other applicable regulations and guidelines. Site visits will be performed for the purpose of inspection of all study related materials and data, subjects' medical records, and eCRFs.

At any time, each site may be audited either by CytRx personnel, or by a contractor acting on behalf of CytRx, or by a regulatory agency such as the FDA.

10.4 Study Medication Accountability

CytRx will provide INNO-206 and doxorubicin required for completion of this study. The recipient will acknowledge receipt of INNO-206 indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study medication dispensed from and returned to the study site are to be maintained. Product accountability will be monitored throughout the study. Upon completion or termination of the study and after inventory by a CytRx monitor or designated representative, all unopened drug is to be returned to CytRx or its representatives in the original containers. Residual solutions should be retained by each site for drug accountability. Unopened returned drug should be shipped as instructed by CytRx. Instructions will be provided in the Study Reference Manual.

10.5 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, laboratory test results, and medication inventory records must be maintained by the Investigator or Institution for the following length of time:

- For a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region
- or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

No study records shall be destroyed without prior authorization from CytRx.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with current US FDA regulations, ICH GCP guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

11.1 Informed Consent Document

CytRx will review the draft ICD before it is finalized and submitted to the IRB/EC. The final IRB approved documents must be provided to CytRx or its representatives for regulatory purposes. If the ICD omits the template provisions authorizing CytRx and its representatives and designees to have access to study participant identifiable health information in accordance with 45 CFR Part 164, a separate written authorization complying with 45 CFR Part 164 must be prepared for review and approval by CytRx or its representatives before use.

The ICD must be signed by the subject before his or her participation in the study. A copy of the ICD must be provided to the subject. If applicable, the informed consent document will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors or authorized regulatory representatives at any time.

11.2 Institutional Review Board/Ethics Committee

This protocol, the ICD, relevant supporting information and all types of subject recruitment or advertisement information must be submitted to the IRB/EC for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB/EC prior to implementing changes in the study, except when necessary to eliminate apparent immediate hazards to human subjects.

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The investigator must also keep the IRB/EC informed of any significant AEs as well as all SAEs.

11.3 Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited.

Information obtained during the conduct of this study will be collected, processed, and transmitted to or for the benefit of CytRx in accordance with applicable law, as discussed below. Information contained therein will be maintained in accordance with applicable law protecting subject privacy and may be inspected by the clinical researcher, the researcher's staff, CytRx and its representatives, to check, process, evaluate, and use the information collected during the study. Processing, evaluation, or use of the information will be performed by a health professional for medical purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional. Information will be transmitted and processed as CytRx may direct, including to CytRx and its representatives in the United States or elsewhere. Information obtained from the study will likely be used by CytRx in connection with the development of the study drug, including possible filing of applications with governmental authorities for marketing approval, and for other pharmaceutical and medical research purposes. The study investigator is obliged to provide CytRx with complete test results and all data developed in this study. This information may be disclosed to other physicians who are conducting similar studies and to the

FDA/applicable regulatory agencies as deemed necessary by CytRx. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission.

All investigators and other research study personnel who process information from the study and are employed by or otherwise affiliated with the Institution are bound by the confidentiality terms of the Clinical Study Agreement between CytRx or its representative and the Institution covering the conduct of this clinical study. Investigators and other personnel should refer to the Clinical Trial Agreement for the specific measures which must be taken to prevent unauthorized or unlawful processing or disclosure of data.

To ensure compliance with current Federal Regulations and the ICH GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, applicable health authorities, CytRx, and the IRB/EC for each study site.

11.3.1 Publications

CytRx intends to pursue publication of the results of the study in cooperation with a lead Investigator, subject to the terms and conditions of the clinical trial agreement between CytRx and Investigators. CytRx approval is required for publication of any data subsets. Final authorship will be determined based on the number of qualified subjects enrolled by each center. Subject names and other personal data relating to an identified or identifiable subject (such as photographs, audio, videotapes, or other factors specific to physical, physiological, mental, economic, cultural or social identity) may not be disclosed in any publication without prior written authorization from CytRx and the subject.

11.3.2 Research Outside the Terms of this Protocol

CytRx has a legal responsibility to report fully to the regulatory authorities all of the results of administration of its investigational drugs.

No investigative procedures other than those described in this protocol shall be undertaken on subjects enrolled in this study (unless required for the care of the subject), without the agreement of the IRB and CytRx. The nature and results of any such procedures must be recorded and reported by a method agreed between CytRx and the Investigator. The consent of the subjects must be obtained before any such procedures are undertaken.

The investigative drug provided to the Investigator for use under this protocol may not be used for any other purpose, including another study, compassionate use, or personal use.

12. APPENDICES

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of Treatment[14]	Every 2 or 3 mo.[13]	Follow Up[12]
Signed informed consent	X									
Review inclusion/exclusion	X	X								
Medical history[1]	X									
Physical examination	X	X	X	X	X	X	X	X[16]	X	
Height (cm)	X									
Weight (kg)	X	X	X	X	X	X	X			
BSA calculation[2]		X	X	X	X	X	X			
Vital signs[3]	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X	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	X	X	X[11]	X	
ECHO (with ejection fraction) or MUGA/cardiac ultrasound	X		X		X		X	X	X	
CBC w/differential & plts[5]	X	X[16]	X	X	X	X	X	X[11]	X	
Coagulation tests (PT, PTT, INR)	X									
Serum chemistries[5, 6]	X	X[16]	X	X	X	X	X	X[11]		
Urinalysis[7]	X							X[11]		
Serum troponin	X	X[16]	X	X	X	X	X	X[11]	X	
Serum/urine pregnancy test	X									
Randomization		X[15]								
INNO-206 or doxorubicin admin administration[17]		X	X	X	X	X	X			
Blood alcohol level[18]		X	X	X	X	X	X			
Concomitant medications	X[9]	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X		
Telephone call										X

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

1. To include concurrent baseline conditions (using NCI CTCAE, version 4.0; see Appendix C), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
2. BSA only needs to be calculated if there has been a change >10% in body weight from Cycle 1-Day 1.
3. Blood pressure, pulse, respiratory rate, and temperature. On days of study drug administration, vital signs will be monitored every 15 min starting immediately prior to INNO-206 or doxorubicin dosing and ending approximately 30 min after completion of infusion.
4. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated). In addition to the CT / MRI scan, tumor size may also be assessed utilizing visual or palpable lesions on physical examination including full assessment of all known metastases (see RECIST 1.1 criteria[29] in Section 8.2)
5. During treatment, if any drug-related and/or clinically significant toxicity occurs, retest frequently until stable or resolving and in accordance with GCP.
6. To include BUN, phosphorus, magnesium, LDH, creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, ALP, AST, ALT, and electrolytes (chloride, sodium, potassium, and bicarbonate).
7. Lab urinalysis to include protein, specific gravity, glucose, and blood.
8. CT/MRI scans should be done every 6 weeks from Cycle 1-Day 1 during treatment. Additional scans may be conducted at other time points if deemed clinically appropriate. Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements. In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.
    a. If CT scan was taken within 28 days prior to first dose, a new scan is not necessary if the scans were performed as qualified by CoreLab. A brain scan is required to exclude brain metastasis if clinically indicated.
9. To include all medications taken within 30 days prior to study enrollment.
10. If not done within the previous 14 days, using same imaging method as Screening.
11. If not done within the previous 14 days. For serum troponin, if not done within the previous 7 days.
12. Follow-up assessments by telephone will be conducted for all subjects every 8 weeks from the time a subject either withdraws from treatment or at disease progression until the subject is either lost to follow-up, passes away, or the Sponsor stops the study.
13. Two months following the End of Treatment scan (for those subjects completing 6 cycles), then every 3 months to disease progression. Also, for those subjects that do not continue on to another therapy. If a subject starts another therapy they should only be followed-up for Overall Survival (footnote 12).
14. When the subject completes all 6 cycles of study medication, or withdraws from treatment prior to completing all 6 cycles for any reason, the following assessments

will be performed within 21-28 days after completing their last dose of study medication.

15. Randomization of subject must be done through the IXRS system at least 5 days prior to the planned Cycle 1-Day 1 visit.
16. Does not need to be repeated if performed within 21 days of Cycle 1-Day 1 visit.
17. If a burning sensation occurs, see Study Reference Manual for recommendations.
18. Blood alcohol levels measured within 15 minutes post-infusion in those subjects receiving INNO-206.

APPENDIX B: ECOG Performance Status Scale

Grade	Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

As published in *Am J Clin Oncol (CCT)*. 1982;5:649-655.

APPENDIX C: Revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (published 28 May 2009)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 can be viewed on-line at the following NCI web site:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX D: New York Heart Association Functional Classifications

Clinical Evaluation of Functional Capacity of Subjects with Heart Disease in Relation to Ordinary Physical Activity

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places subjects in one of four categories based on limitations during physical activity:

Class	Subject Symptoms
I (mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II (mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III (moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV (severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reference: Bruce RA. *Mod Concepts Cardiovasc Dis.* 1956;25(4):321-326 (Modified from New York Heart Association, 1953.)

APPENDIX E: 2006 Update of ASCO Practice Guideline Recommendations for the Use of White Blood Cell Growth Factors: Guideline Summary

Setting/Indication	Recommendation
Primary prophylaxis	Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For "dose-dense" regimens, CSF is required and recommended. Clinical trial data support the use of CSF when the risk of FN is in the range of 20% or higher.
Primary prophylaxis: Special circumstances	Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age > 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor-producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate, even with regimens with FN rates of < 20%.
Secondary prophylaxis	Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
Therapeutic use: Afebrile neutropenia	CSF should not be routinely used for patients with neutropenia who are afebrile.
Therapeutic use: Febrile neutropenia	CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 × 109/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
Dose intensity/density of chemotherapy	Dose-dense regimens should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data.
Adjuncts to progenitor-cell transplantation	Administration of CSF to mobilize PBPC often in conjunction with chemotherapy, and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.
AML: Initial or repeat induction chemotherapy	CSF use following initial induction therapy is reasonable, though there has been no favorable impact on remission rate, remission duration, or survival. Patients > 55 years of age may be most likely to benefit from CSF use.
AML: CSF for priming effects	Use of CSF for priming effects is not recommended.
AML: Consolidation chemotherapy	CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of

	hospitalization in some patients receiving intensive postremission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. As yet there is no information about the effect of longer-acting pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical trials.
MDS	Intermittent administration of CSF may be considered in a subset of patients with severe neutropenia and recurrent infection.
ALL	CSF administration is recommended after the completion of the initial first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of < 1,000/mm^3 by approximately 1 week.
Acute leukemia in relapse	CSF should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia.
Radiotherapy ± chemotherapy	CSF should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSF may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.
Older patients	Prophylactic CSF for patients aged ≥ 65 years with lymphoma treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.
Pediatric patients	As in adults, the use of G-CSF is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of G-CSF for secondary prophylaxis or for therapy should be limited to high-risk patients. However, the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with G-CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the specific use of G-CSF in children with ALL should be considered carefully.
Comparative clinical activity of G-CSF and GM-CSF	No guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents. Further trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of GCSF and GM-CSF.
Treatment for radiation injury	Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.

Abbreviations: CSF, colony-stimulating factors; FN, febrile neutropenia; PBPC, peripheral-blood progenitor cell; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, filgrastim; GM-CSF, sargramostim; pegylated G-CSF, pegfilgrastim.

APPENDIX F: Lown Classification

0	None
1	Unifocal; < 30/h
2	Unifocal; ≥ 30/h
3	Multiform
4A	2 consecutive
4B	≥ 3 consecutive
5	R-on-T phenomenon

APPENDIX G: Medications with High Incidence of QT Prolongation

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Ketoconazole	Venlafaxine		
	Itraconazole			

Reproduced from http://www.uspharmacist.com/content/t/cardiovascular/c/10396/

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APPENDIX H: Extravasation Guidelines

On intravenous administration of doxorubicin or INNO-206, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 minutes, q.i.d. for 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

APPENDIX I: Medications That Interact with Ethanol

CLASS/DISORDER	GENERIC NAME (not exhaustive list)
Angina, coronary heart disease	isosorbide, nitroglycerin
Antianxiety and Antiepileptics	lorazepam, clonazepam, chloridazepoxide, paroxetine, diazepam, alprazolam
Antidepressants	clomipramine, citalopram, trazodone, venlafaxine, amitriptyline, escitalopram, fluvoxamine, desipramine, paroxetine, fluoxetine, nefazodone, bupropion, sertaline
Diabetes	metformin, glyburide, tolbutamide
High blood pressure	quinapril, doxazosin, clonidine, losartan
Narcotics	morphine, codeine, vicodin, percocet, demerol, dilaudid

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Statistical Analysis Plan

Sponsor Name:	CytRx Corporation
Protocol Number and Title:	INNO-206-P2-STS-01 A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma
Protocol Version and Date:	Amendment 2; April 15, 2012
INC Research Project Code:	12148
Author(s):	Yunbin Zhang, Sr. Biostatistician
SAP Version:	1.0 Amendment
SAP Version Date:	11-SEP-2013
SAP Amendment Date:	20-JAN-2015

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Statistical Analysis Plan

Version: 1.0 Amendment **Version Date:** 20-Jan-2015

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
INC Research	
Lead Biostatistician Yunbin Zhang, Sr. Biostatistician	21-Jan-2015 Date (dd-Mmm-yyyy)
Senior Reviewing Biostatistician John Zhang, Manager, Biostatistics	21-Jan-2015 Date (dd-Mmm-yyyy)
Lead Statistical Programmer Parasuram Kapri, Sr. Statistical Programmer	21-Jan-2015 Date (dd-Mmm-yyyy)
Project Leader Jennifer Rowe, Project Manager	21-Jan-2015 Date (dd-Mmm-yyyy)
CytRx Corporation	
Dan Levitt, M.D. Chief Medical Officer	21-Jan-2015 Date (dd-Mmm-yyyy)
Scott Wieland, Ph.D. Senior Vice President, Drug Development	21-JAN-2015 Date (dd-Mmm-yyyy)

Statistical Analysis Plan

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Statistical Analysis Plan

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALP	Alanine Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
CMH	Cochran-Mantel-Hanszel
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVI	Intravenous infusion
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MUGA	Multiple-gated Acquisition
NCI	National Cancer Institute
NE	Not Evaluable

Statistical Analysis Plan

Abbreviation	Description
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM-IV Disorders
SD	Stable Disease
SOC	System Organ Class
STS	Solid Tissue Sarcoma
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

2. PURPOSE

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to support the completion of the Clinical Study Report (CSR) for protocol INNO-206-P2-STS-01. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective CSR.

2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2. TIMINGS OF ANALYSES

Final Analysis: The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study.

There is a Data Safety Monitoring Board (DSMB) for this study. Details are described in the DSMB charter.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this study is to determine the preliminary efficacy of administration of INNO-206 compared to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma (STS) (in Indian subjects with metastatic or unresectable STS only) as measured by progression-free survival (PFS), progression-free survival at 4 and 6 months, tumor response, and overall survival (OS).

3.2. SECONDARY OBJECTIVE(S)

The secondary objective of this study is to evaluate the safety of INNO-206 compared to doxorubicin in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, multiple-gated acquisition (MUGA) scans/cardiac ultrasound evaluations, electrocardiogram (ECG) results, and weight.

3.3. STUDY DESIGN

BRIEF DESCRIPTION

This is a phase 2b, randomized, open-label, prospective, multicenter study comparing treatment with INNO-206 to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas (in Indian subjects with metastatic or unresectable STS only) who have not been previously treated with any chemotherapy except potentially as adjuvant or neoadjuvant chemotherapy, (including≤ 3 cycles or <225 mg/m2 doxorubicin or Doxil®) and no evidence of tumor recurrence has occurred for at least 12 months. One hundred five (105) subjects will be enrolled and randomized 2:1 to receive either INNO-206 or doxorubicin. INNO-206 at a dosage of 350 mg/m^2 (doxorubicin equivalents of 260 mg/m^2) will be administered as a 30 minute IVI on Day 1 of each cycle to approximately 70 subjects. Doxorubicin (75 mg/m^2) will be administered to approximately 35 subjects per the instructions outlined in the package insert (Study Reference Manual) on Day 1 of each cycle. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be monitored every 15 min starting immediately prior to either INNO-206 or doxorubicin dosing and ending approximately 30 min after the completion of the infusion.

An individual cycle of therapy will be defined as a 3-week (21-day) period. Cycles will be repeated every 3 weeks. Multiple cycles may be administered until the subject is withdrawn from therapy or until a maximum of 6 cycles are administered. After 6 cycles of therapy, additional cycles may only be administered following consultation with the CytRx Medical Monitor.

3.4. SUBJECT SELECTION

Approximately one hundred and five (105) subjects will be recruited from approximately 30 study centers in the United States, Hungary, Romania, Ukraine, Russia, India and Australia. Up to 32 subjects may be enrolled in India, with the remaining subjects distributed in other locations.

3.4.1. Inclusion Criteria

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

1. Age between 15-80 years (US only), 18 – 65 years (for India only), and 18-80 (rest of world (ROW)), 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, unresectable, and/or metastatic soft tissue sarcoma of intermediate or high grade, for India only. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma of intermediate or high grade for the rest of world (ROW).

4. Capable of providing informed consent and complying with trial procedures.

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

6. Life expectancy >12 weeks.

7. Measurable tumor lesions according to Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria.

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. 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 that ensures the subject will be able to keep all study-related appointments.

3.4.2. 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/m2 of doxorubicin or Doxil®.

3. Palliative surgery and/or radiation treatment less than 4 weeks prior to Randomization.

4. Exposure to any investigational agent within 30 days of Randomization.

5. Current Stage 1 or 2 soft tissue sarcomas.

6. Current evidence/diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma, Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas and unresectable low grade liposarcomas.

7. Central nervous system metastasis

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/mm3, platelet concentration <100,000/mm3, hematocrit level <25% for females or <27% for males, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN, and albumin <2.0 g/dL.

10. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.

11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.

12. Baseline corrected QT (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 human immunodeficiency virus (HIV) infection.

16. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.

17. Major surgery within 3 weeks prior to 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.

3.5. DETERMINATION OF SAMPLE SIZE

Power calculations and subject numbers were calculated based on the progression-free survival endpoint. Historical data have shown that the PFS in this population treated with doxorubicin chemotherapy is approximately 4.4 months. Based on the use of a two-sided test at the alpha=0.05 level of significance, a total of 89 progressions will be required for at least 83% power to detect a PFS duration for INNO-206 of 8.5 months. Assuming an 15 month accrual period and 12-month follow-up, further if the dropout rate for INNO-206 treatment group and doxorubicin are 20% each at the end of study (Month 27) respectively and also dropouts follow the exponential distribution, 70 subjects in the INNO-206 treatment group and 35 subjects in the doxorubicin group will be needed to achieve the total of 89 progressions. Therefore, a total of 105 subjects are required according to a randomization ratio of 2:1 (INNO-206: doxorubicin).

3.6. TREATMENT ASSIGNMENT & BLINDING

This is a phase 2b, randomized open-label trial, with the identity of the treatment known to the subjects, Investigators, and Sponsor. Subjects will be randomized through the IXRS system at least five days prior to the planned Cycle 1-Day 1 visit in a 2:1 ratio (INNO-206:doxorubicin) across all study sites. Randomization will be stratified by the initial performance status (ECOG 0-1 vs. 2) and whether subjects had received either prior adjuvant or neoadjuvant chemotherapy or no prior chemotherapy. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study.

3.7. ADMINISTRATION OF STUDY MEDICATION

INNO-206 will be administered by intravenous infusion (IVI) over a period of approximately 30 minutes into a peripheral line (or central line, if available) once every 3 weeks for a maximum of 6 cycles. After 6 cycles of therapy, additional cycles may only be administered following consultation with the CytRx Medical Monitor. INNO-206 infusion should be completed within 2 hours after reconstitution and dilution into Lactated Ringer's solution. Treatment must be administered in a hospital, clinic or other out-patient setting appropriate for chemotherapeutic infusions. The solution for infusion will be prepared at each investigational site by trained personnel.

Detailed guidelines for the preparation and administration of INNO-206 or doxorubicin are provided in the Study Reference Manual.

3.8. STUDY PROCEDURES AND FLOWCHART

The schedule of treatment and evaluations is presented in Table 1.

Statistical Analysis Plan

Table 1. Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Additional Cycles after Cycle 6	End of Treatment[14]	Every 2 or 3 mo.[13]	Follow Up[12]
Signed informed consent	X										
Review inclusion/exclusion	X	X									
Medical history[1]	X										
Physical examination	X	X	X	X	X	X	X	X	X[16]	X	
Height (cm)	X										
Weight (kg)	X	X	X	X	X	X	X	X			
BSA calculation[2]		X	X	X	X	X	X	X			
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	X	X		
CT/ MRI scan / tumor measurements[4]	X[8a]			X[8]		X[8]		X[6]	X[10]	X	
ECG	X	X	X	X	X	X	X	X	X[11]	X	
ECHO (with ejection fraction) or MUGA/cardiac ultrasound	X		X		X		X	X	X	X	
CBC w/differential & plts[5]	X	X[16]	X	X	X	X	X	X	X[11]	X	
Coagulation tests (PT, PTT, INR)	X										
Serum chemistries[5, 6]	X	X[16]	X	X	X	X	X	X	X[11]		
Urinalysis[7]	X								X[11]		
Serum troponin	X	X[16]	X	X	X	X	X	X	X[11]	X	
Serum/urine pregnancy test	X										
Randomization		X[15]									
INNO-206 or doxorubicin admin administration[17]		X	X	X	X	X	X	X			
Blood alcohol level[18]		X	X	X	X	X	X	X			
Concomitant medications	X[9]	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X		
Telephone call											X

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1.

1. To include concurrent baseline conditions (using NCI CTCAE, version 4.0; see Appendix C), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
2. BSA only needs to be calculated if there has been a change >10% in body weight from Cycle 1-Day 1.
3. Blood pressure, pulse, respiratory rate, and temperature. On days of study drug administration, vital signs will be monitored every 15 min starting immediately prior to INNO-206 or doxorubicin dosing and ending approximately 30 min after completion of infusion.
4. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated). In addition to the CT / MRI scan, tumor size may also be assessed utilizing visual or palpable lesions on physical examination including full assessment of all known metastases (see RECIST 1.1 criteria[29] in Section 8.2)
5. During treatment, if any drug-related and/or clinically significant toxicity occurs, retest frequently until stable or resolving and in accordance with GCP.
6. To include BUN, phosphorus, magnesium, LDH, creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, ALP, AST, ALT, and electrolytes (chloride, sodium, potassium, and bicarbonate).
7. Lab urinalysis to include protein, specific gravity, glucose, and blood.
8. CT/MRI scans should be done every 6 weeks from Cycle 1-Day 1 during treatment. Additional scans may be conducted at other time points if deemed clinically appropriate. Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements. In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.
    a. If CT scan was taken within 28 days prior to first dose, a new scan is not necessary if the scans were performed as qualified by BioClinica (CoreLab). A brain scan is required to exclude brain metastasis if clinically indicated.
9. To include all medications taken within 30 days prior to study enrollment.
10. If not done within the previous 14 days, using same imaging method as Screening.
11. If not done within the previous 14 days. For serum troponin, if not done within the previous 7 days.
12. Follow-up assessments by telephone will be conducted for all subjects every 8 weeks from the time a subject either withdraws from treatment or at disease progression until the subject is either lost to follow-up, passes away, or the Sponsor stops the study.
13. Two months following the End of Treatment scan (for those subjects completing 6 cycles), then every 3 months to disease progression. Also, for those subjects that do not continue on to another therapy. If a subject starts another therapy they should only be followed-up for Overall Survival (footnote 12).
14. When the subject completes all 6 cycles of study medication, or withdraws from treatment prior to completing all 6 cycles for any reason, the following assessments will be performed within 21-28 days after completing their last dose of study medication.
15. Randomization of subject must be done through the IXRS system at least 5 days prior to the planned Cycle 1-Day 1 visit.
16. Does not need to be repeated if performed within 21 days of Cycle 1-Day 1 visit.
17. If a burning sensation occurs, see Study Reference Manual for recommendations.
18. Blood alcohol levels measured within 15 minutes post-infusion in those subjects receiving INNO-206.

4. ENDPOINTS

Efficacy and safety profiles of INNO-206 will be determined using the following endpoints.

4.1. PRIMARY EFFICACY ENDPOINT

- Progression-free survival

4.2. SECONDARY EFFICACY ENDPOINTS

- Overall survival
- Progression-free survival at 4 month
- Progression-free survival at 6 month
- Overall response rate defined per RECIST 1.1 criteria

4.3. SAFETY ENDPOINTS

Safety will be assessed by evaluating the following endpoints:

- Adverse Events (AEs)
- Laboratory tests
- Extent of exposure
- Vital signs
- Electrocardiogram (ECG)
- Physical Exam
- Cardiac Evaluation
- Concomitant medications

5. ANALYSIS SETS

5.1. INTENT-TO-TREAT (ITT) POPULATION

The ITT population is defined as all subjects who are randomized to a treatment group in the study.

5.2. SAFETY POPULATION

The safety population will include all subjects who received any amount of study drug. The safety population will be used in the safety analyses.

5.2.1. Protocol Deviations

Major protocol deviations are defined as those that potentially impact subject safety and/or data integrity, and may include but are not limited to the following:

- Dosing/randomization errors
- Procedural errors
- Major violations of inclusion or exclusion criteria as determined by the Medical Monitor (INC)
- Delays of greater than 14 days in scheduled CT scans

All major protocol deviations will be summarized and listed for the study using safety population.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

INC Research will be responsible for reporting the demographic, efficacy and safety analysis. The ITT population will be used for the disposition table. Demographic and baseline characteristics will be tabulated using ITT populations. The safety population will be used for all safety analyses, and the ITT population will be used for the efficacy analyses.

- All analyses and summaries will be produced using SAS® version 9.3 (or higher).
- For most summary statistics, data will be analyzed and displayed by treatment groups of Doxorubicin and INNO-206.
- Unless otherwise specified, continuous variables will be summarized with descriptive statistics including n, mean, standard deviation, median, and minimum and maximum values. All categorical/qualitative data will be presented using absolute and relative frequency counts and percents. Shift tables will be produced for some assessments and will contain counts and percents of subjects in each cross-classification level of baseline versus post-baseline assessment. Only subjects with a baseline will be included in these tables, but a missing category will be permitted for post-baseline values. All statistical tests and confidence intervals will be 2-sided and will be set at $\alpha = 0.05$.
- The listings will include all subjects in the database regardless of analysis population membership. In general, the subject listings will be sorted by treatment group, subject number and assessment date (and time) if applicable.
- Measurements from subjects excluded from the analysis populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the subject listings. Data from extra measurements will be included when calculating baseline and/or selecting best or worst result.

6.2. EFFICACY DATA HANDLING

Efficacy assessments will be based on the change from baseline in tumor measurements obtained from serial radiographs and clinical measurements (e.g., CT scans) performed at the following time points:

- Baseline
- Tumor Response will be monitored every 6 weeks from Cycle 1-Day 1 during treatment, at end of treatment, 2 months following the End of Treatment scan (for those subjects completing 6 cycles), then every 3 months to disease progression. For those subjects that leave the study prior to completing Cycle

6, and who do not start another therapy, they can be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. However, if a subject receives another therapy, they should only be followed for overall survival [OS].

In addition to radiographic tumor assessments, survival status will also be used for efficacy assessments. The modality used to obtain tumor measurements will depend on tumor location, and the same modality and equipment should be used for obtaining serial tumor measurements. Tumor measurements will be obtained in accordance with RECIST criteria Version 1.1. Refer to Section 8.2 of the protocol for detailed guidance on measurable and non-measurable lesions, methods of measurement, and baseline documentation of target and non-target lesions. The final assessments of tumor measurements will be performed by an Independent Radiology Reviewer (BioClinica, formerly CoreLabs) and will be the prevailing assessment for tumor response and disease progression.

6.3. KEY DEFINITIONS

6.3.1. Baseline Value

Unless otherwise specified, baseline is the last non-missing observation before the start of first study drug infusion.

6.3.2. Adverse Events

An adverse event (AE) is any unfavourable medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. All AEs occurring after any administration of the study medication will be followed until the event resolves, until the subject begins alternative treatment, or until 30 days after the last dose of study medication.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE.

6.3.3. Study Day

Study day is defined as the number of days from the study reference date to the event or visit date, inclusive of both the reference date and event or visit date. Programmatically, it is calculated as follows: Study Day = Event or Visit Date – Reference Date + 1.

Hence, the reference date is referred to as day 1. The previous day is day -1.

6.3.4. Treatment Emergent Adverse Event (TEAE)

TEAE is defined as any AE occurring at or after the initial administration of study agent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent.

If the event start date is partially or completely missing, then the event will be considered to be treatment emergent unless from the information available the event could only have been prior to the initial administration of study agent. In practice, this means that the event will be treatment emergent unless any one or both of the following 2 conditions hold:

- The year of AE start falls before the year of first dose, or if the year of AE start date is the same as the year of first dose, month of AE start falls before the month of first dose.
- The AE end date falls before first dose date. The year of AE end falls before the year of first dose, or if the year of AE end is the same as the year of first dose, the month of AE end falls before the month of first dose.

6.3.5. Efficacy Response Definitions

Best Overall Response

Best overall response is defined as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for tumor progression, the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of measurement criteria.

Best overall response will be the best response recorded with the latest assessment date from BioClinica; while the best response recorded from the start of the treatment until the date of withdrawal (discontinuation) from the study from CRF data will be the best overall response.

Overall Tumor Response

The overall tumor response rate is defined as the total proportion of subjects who have an objective tumor response (complete response (CR) + partial response (PR)). Rates for the individual categories of response (CR, PR, stable disease (SD), progressive disease (PD) and not evaluable (NE)) will also be determined.

Progression-free Survival

PFS is defined as the time from enrollment (i.e., date of randomization) to first documentation of objective tumor progression or to death due to any cause in the

absence of previous documentation of objective tumor progression. PFS will be censored at the last date the subject was known to be progression-free in subjects who do not have objective tumor progression and who are: 1) still on study at the time of an analysis; 2) are given anti-tumor treatment other than the study treatment; or 3) are removed from study follow-up prior to documentation of objective tumor progression. As such, missing data will be censored without any further imputation.

If there are no date of progression recorded from BioClinica, the progression-free for the subjects will be censored at the date of discontinuation of study (if subjects discontinue due to death, they will not be censored); Similarly, if subjects don't have overall tumor response of progressive disease in the CRF data, and the reasons for discontinuing the study are neither progressive disease nor death, the subjects will be censored at the date of discontinuation of study for progression-free survival.

Overall Survival

Overall survival is defined as the time from enrollment (i.e., date of randomization) to date of death. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive. As such, missing data will be censored without any further imputation.

6.4. MISSING DATA

Missing or dropout data will not be imputed in the data analysis.

6.5. VISIT WINDOWS

If an observation is missing at a specific scheduled visit, the value at that visit will be set to missing.

6.6. MULTICENTER CONSIDERATIONS

No adjustment will be made for multicenter considerations.

6.7. MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustment will be made for multiplicity.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

A detailed description of subject disposition will include:

- Subjects who were randomized
- Subjects who were randomized but not dosed with study drug
- Subjects who were in the safety population
- Subjects who completed the planned 6 cycles
- Subjects who discontinued from the treatment early
- Subjects with the primary reason for early discontinuation from the treatment
- Subjects who were not followed up any longer, that is, subjects still in the study did not have PD at the time of database lock.
- Subjects who discontinued from the study early
- Subjects with the primary reason for early discontinuation from the study

Disposition will be summarized for all randomized subjects. Assignment to the analysis populations (ITT and Safety) as well as subjects who discontinued early from the study will be summarized by treatment group and overall. The primary reason for early discontinuation from the treatment and study will also be presented.

A listing of disposition will be provided for all subjects.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics (gender, race, ethnicity, age (years), weight (kg), height (cm), and baseline body surface area (BSA, m^2)) will be summarized by treatment group and overall. Gender, race, and ethnicity will be summarized by using summary statistics for categorical variables. Age, weight, height and baseline BSA will be summarized by using summary statistics for continuous variables.

Age will be calculated as the number of years between date of birth and date of study day 1.

Age at Study day 1 = (Study day 1) visit date - date of birth + 1) / 365.25 and truncated to complete years.

Baseline characteristics (initial performance status (ECOG 0-1 vs. 2), prior

chemotherapy status (no prior chemotherapy vs. prior adjuvant/ neoadjuvant chemotherapy) as well as pregnancy status will also be summarized by using summary statistics for categorical variables.

7.3. MEDICAL HISTORY, PRIOR THERAPIES AND PRIOR SURGERY

7.3.1. Medical History

Past and concomitant diseases will be coded by system organ class (SOC) and preferred term (PT) by using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Medical conditions are graded per CTCAE version 4.0 (1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, 5=death) on the CRF. The count and percentage of subjects under each history term, coded by SOC and PT, will be summarized by treatment. The summary will be sorted by counts of total subjects, from both treatment groups, under each SOC and by PT within each SOC. All reported medical history will be listed by treatment group.

7.3.2. Prior Systemic Therapy

Prior systemic therapy information will be presented in a listing.

7.3.3. Prior Radiotherapy

Prior radiotherapy information will be presented in a listing.

7.3.4. Prior Surgery

Prior surgery information will be presented in a listing.

7.4. PRIOR AND CONCOMITANT MEDICATION

All medications will be coded using the World Health Organization (WHO) drug Anatomical Therapeutic Chemical (ATC) classification system. ATC levels 2 and 4 will be used in the summary tables.

As both prior and concomitant medications are collected on the same CRF page, the following rule will be used to distinguish prior versus concomitant medication:

- Medications with a stop date prior to the first date of study drug will be considered prior medications.
- Medications with a start date or stop date on or after the first date of study drug will be considered concomitant medications.

- Medications with completely missing stop dates will also be considered as concomitant medications.

For prior and concomitant medications which are indistinguishable using the above rules because of incomplete dates, they will be considered concomitant medications using the following algorithm:

- Day and month are missing and the year is equal to or after the year of the first treatment date;
- Day is missing and the year is after the year of the first infusion date;
- Day is missing and the year is equal to the year of the first infusion date and the month is equal to or after the month of the first infusion date;
- Year is missing; or
- Complete date is missing.

For the summary tables, the count and percentage of subjects under each medication, coded by ATC Class 2 and 4, will be summarized by treatment. The summary will be sorted by counts of total subjects, from both treatment groups, under ATC Class 2 and by ATC Class 4 within each ATC Class 2. If a subject has taken a prior or concomitant medication more than once, the subject will be counted only once under each ATC Class.

A list of G-CSF concomitant medications of interest includes Neulasta (pegfilgrastim), Neupogen (filgrastim), Grafeel, Neukine, Emgrast, Religrast, Zarzio, Nufil. Duration (days) of applying each G-CSF concomitant medications will be descriptively summarized by treatment groups and overall.

Duration in days will be derived as the stop date of medications –start date of medication +1; if the stop date is recorded as 'ONGOING', the date of progression or discontinuation of study recorded at CRF 'end of study' page will be used as the stop date. Medications with partial or missing start date or stop date will not be summarized.

All reported medications (prior and concomitant) will be listed by treatment group. A flag will be included in the listing to distinguish concomitant versus prior medications.

8. EFFICACY ANALYSES

Efficacy will be evaluated based on the assessment of tumor response. The ITT population will be used for the primary efficacy analysis and subgroup analyses. The ITT population will also be used for all secondary efficacy analyses unless otherwise specified. Summary will be presented by treatment group.

The tumor response assessment both from BioClinica and recorded on CRF will be analyzed separately, and the analysis results from BioClinica assessments are considered as primary.

8.1. PRIMARY EFFICACY ANALYSES

The primary efficacy endpoint is the progression-free survival for subjects with STS. The goal of the trial is to demonstrate the superiority of INNO-206 compare with doxorubicin in terms of progression free survival. Let HR_{pfs} be the hazard ratio of INNO-206 vs. doxorubicin in terms of progression free survival, then the hypothesis will be:

H_0: $HR_{pfs}=1$ vs.

H_1: $HR_{pfs}\neq 1$

8.1.1. Statistical Methodology

The primary efficacy endpoint will be analyzed using log-rank test stratified by the initial performance status and subjects had received prior chemotherapy. For the primary treatment comparison, the treatment effect is statistically significant if the 2-sided log rank $p<0.05$. The median progression free survival time along with its 2-sided 95% confidence interval will be estimated using Kaplan Meier method. Kaplan Meier estimates for the progression free survival distribution will be provided by treatment group.

In addition, a Cox regression model stratified by the initial performance status and subjects had received prior chemotherapy will be used to estimate the hazard ratio of INNO-206 vs. doxorubicin and its 2-sided 95% confidence interval. The exact tie-handling method will be used for this model.

8.1.2. Subgroup Analyses

For the primary efficacy endpoint the following subgroup analyses will be performed:

- Initial performance status (ECOG 0-1 vs. 2)

If less than 10% subjects have ECOG=2 at baseline, then this subgroup analysis will not be done.

- Prior Chemotherapy (no prior chemotherapy vs. prior adjuvant/neoadjuvant chemotherapy)
- Region (America, Europe and Asia(including Australia))
- Tumor Type (Leiomyosarcoma, Liposarcoma, Fibrosarcoma and Variants, Synovial, Other)
- Age Group (>=50 years vs. <50 years)
- Sex (Male vs. Female)
- Race (Caucasian vs. Other)
- Number of Cycle Subject Received (>=4 Cycles vs. <4 Cycles)
- Best Overall Response (CR+PR vs. SD)
- Subjects with Grade 3 and 4 Neutropenia

8.2. SECONDARY EFFICACY ANALYSES

8.2.1. Overall Survival

Overall survival will be analyzed using the same statistical model as the one used for the primary efficacy endpoint. The median survival time along with its 2-sided 95% confidence interval will be estimated using Kaplan Meier method. Kaplan Meier estimates for the progression free survival distribution will be provided by treatment group.

In addition, a Cox regression model stratified by the initial performance status and subjects had received prior chemotherapy will be used to estimate the hazard ratio of INNO-206 vs. doxorubicin and its 2-sided 95% confidence interval. The exact tie-handling method will be used for this model. The proportionality of the Cox regression model will be examined using graphical method and/or other inferential methods as appropriate.

The overall survival will also be performed on the following subgroup analyses:

- Initial performance status (ECOG 0-1 vs. 2)

- Prior Chemotherapy (no prior chemotherapy vs. prior adjuvant/neoadjuvant chemotherapy)
- Region (America, Europe (including India))
- Tumor Type (Leiomyosarcoma, Liposarcoma, Fibrosarcoma and Variants, Synovial, Other)

8.2.2. Progression-free Survival at 4 and 6 Month

The progression free survival rates for each treatment group and their difference at 4 months and 6 months, taking the randomization date as the reference date, along with their 2-sided 95% confidence intervals will be estimated using Kaplan Meier method. The test statistic is a quotient whose numerator is the difference of survival rates at 4 months and 6 months. The denominator is found by first squaring each group's standard error by the Greenwood formula at 4 months and 6 months, and summing the result quantity, then take the square root. The p-value is found by comparing the quotient to standard normal distribution.

8.2.3. Overall Response

The overall response (CR+PR) rate for INNO-206 and doxorubicin will be tested using Cochran-Mantel-Hanszel (CMH) test stratified by initial performance status and whether subjects had received prior chemotherapy. The difference of overall response along with the 95% confidence interval will also be provided.

The count and percentage of subjects with overall response will be summarized by treatment. A similar summary table will present the count and percentage of subjects for individual categories of response (CR, PR, SD, PD and NE), as well as subjects with responses of SD or better.

The overall response will also be performed on the same subgroup analyses used for the overall survival.

8.3. OTHER EFFICACY ANALYSES

8.3.1. ECOG

If greater than or equal to 10% of subjects, regardless the treatment, have ECOG status equal to 2 at baseline, the summary will be performed as described below, otherwise, no summary for ECOG.

A descriptive summary table will be created for the ITT population to show the count and percentage of subjects with each ECOG status at each visit, cross-tabulated by baseline ECOG Status.

8.3.2. Tumor Size

The sum of diameters for target lesions will be summarized by assessment time point along with the change from baseline and percent change from baseline. In the case of multiple assessments with the same best response, the earliest assessment will be used.

The greatest reduction (the smallest measurement among all available assessment visits) from baseline in the sum of diameters for the target lesions will also be descriptively summarized by treatment groups and overall. The waterfall plot of greatest decrease in sum of diameters will also be provided.

The summary table will be presented for the ITT population.

9. SAFETY

Safety will be assessed on the basis of the following parameters assessed over the duration of the study:

- Treatment emergent adverse event (TEAE)
- Ability to remain on assigned treatment (tolerability)
- Laboratory data
- ECG parameters
- Physical examinations
- Vital signs
- MUGA/cardiac ultrasound evaluations
- Use of concomitant medications

All safety analyses will be based on the safety population.

9.1. EXTENT OF EXPOSURE

A descriptive summary table will be created to analyze the exposure to INNO-206 and doxorubicin. Summaries will include total exposure (mg), dose intensity, relative intensity, total cycle received, subjects with dose reductions and subjects with dose interruption.

Dose intensity is expressed as mg/ m^2/cycle and derived as total exposure (mg) divided by average BSA measurements recorded in all cycles and by the number of cycles that study drug are administered. Relative intensity (doxorubicin equivalents) for INNO-206 will be calculated as dose intensity (mg/ m^2/cycle) multiply (260/350).

Total exposure, dose intensity, and relative intensity will be summarized as continuous variables using descriptive statistics. Subjects with dose reduction and dose interruption will be summarized as categorical variables using count and percentage. Total cycle received will be summarized both as continuous and categorical variables.

Dosing and exposure data will also be presented in a listing.

9.2. TREATMENT COMPLIANCE

The number and percent of subjects who complete each cycle will be summarized by treatment group using safety population.

9.3. ADVERSE EVENTS

TEAEs will be coded by using the MedDRA. The System Organ Class (SOC) and Preferred Term (PT) will be used for summary tables.

All TEAEs will be graded by using NCI CTCAE version 4.0 as:

- Grade 1 (mild)
- Grade 2 (moderate)
- Grade 3 (severe)
- Grade 4 (life threatening or disabling)
- Grade 5 (death related to AE).

For TEAEs not contained within NCI CTCAE version 4.0, the Investigator will assess the severity/grade of an AE according to the five grades above.

9.3.1. An overall summary table of TEAEs by treatment will be produced for the following categories:

- Number and percent of patients reporting a TEAE
- Number and percent of patients reporting a treatment-related TEAE
- Number and percent of patients reporting a severe or worse TEAE (Grade >= 3)
- Number and percent of patients reporting a treatment-related severe or worse TEAE (Grade >= 3)
- Number and percent of patients reporting a serious TEAE
- Number and percent of patients reporting a treatment-related serious TEAE
- Number and percent of patients reporting a TEAE leading to death
- Number and percent of patients reporting a TEAE leading to discontinuation or interruption of study drug

Adverse events will be summarized by treatment group and overall for subjects in the safety population. The following summaries of adverse events will be provided:

- All TEAEs by MedDRA SOC and PT
- All treatment-related TEAEs by MedDRA SOC and PT
- Serious TEAEs by MedDRA SOC and PT
- Treatment-related serious TEAEs by MedDRA SOC and PT
- TEAEs resulting in discontinuation or interruption of study drug, by MedDRA SOC and PT
- TEAEs resulting in death, by MedDRA SOC and PT
- TEAEs by worst CTCAE grade by MedDRA SOC and preferred term. Missing grades will be assumed as grade 3 (‘severe’).
- TEAEs by relationship to study drug by not related (includes unrelated and unlikely) or related (includes possible and probable) by MedDRA SOC and preferred term. Missing relationships will be assumed as ‘probable’.

- Most frequent TEAEs (>=5%) by MedDRA SOC and PT
- TEAEs by PT only. This table will be sorted in descending order.
- The worst TEAEs with Grade 3 and Grade 4 that related to study drug by MedDRA SOC and PT
- Frequency and percentage of grade 3 and 4 neutropenia, thrombocytopenia and anemia TEAEs by cycle.

  TEAEs will be assigned to a cycle if TEAEs with start date on or after the treatment date of a cycle but before the treatment date of the subsequent cycle. TEAEs will be assigned to the last cycle if their start date on or after the treatment date of the last cycle. TEAEs with Partial or missing start date will not be assigned to any cycles.
- The following listings of adverse events will be provided:
  - All AEs
  - Adverse events resulting in discontinuation of study drug
  - Deaths (if any)
  - Serious adverse events
  - All severe TEAEs (Grade > = 3)

In the summary tables patients may be counted under multiple system organ classes and preferred terms, but for each system organ class and preferred term, patients are only counted once. If a patient has the same adverse event on multiple occasions, the highest severity (grade 5 > grade 4 > grade 3 > grade 2 > grade 1) or drug relationship (probably > possibly > unlikely > unrelated) recorded for the event will be presented.

9.4. LABORATORY EVALUATIONS

Clinical laboratory test result (hematology, chemistry, urinalysis, serum troponin, and blood alcohol level) and their changes from baseline will be summarized by analysis visit using descriptive statistics. The laboratory test result will be reported as “Normal”, “Abnormal, Not Clinically Significant”, or “Abnormal, Clinically Significant” with respect to relevant abnormalities by the investigator. A shift table comparing the laboratory test results (hematology and chemistry) over the study visits to baseline measure will be presented.

All summary will be present separately for hematology, chemistry, urinalysis, serum troponin, and blood alcohol level.

For the laboratory results collected in conventional units will be converted to SI units for all the summaries and listings.

In additional, Anion Gap (mmol/L), which is calculated as Sodium (mmol/L) – [Bicarbonate (mmol/L) + Chloride (mmol/L)], will be summarized by analysis visit using descriptive statistics. Number and percent of patients that has an Anion Gap > 16 mmol/L will also be summarized.

All laboratory results will be summarized as observed and no missing value will be imputed.

9.5. ECG

A 12-lead ECG will be performed on the days indicated in Table 1. The overall ECG assessment will be reported as "Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant" with respect to relevant abnormalities by the investigator. A shift table comparing the ECG assessment over the study visits to baseline measure will be presented.

Electrocardiogram data will be provided in a data listing.

9.6. PHYSICAL EXAMINATION

Physical examination results will be presented in a data listing only.

9.7. VITAL SIGNS

Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be monitored every 15 minutes starting immediately prior to the INNO-206 or doxorubicin infusion and ending approximately 30 minutes after completion of the infusion.

Changes in vital signs of greater than or equal to two standard deviations from baseline will be summarized at each post-baseline visit and time point by treatment. The standard deviation will be calculated based off of the baseline data for the treatment group and the change will be calculated from the subject's baseline and post-baseline results.

No missing vital sign value will be imputed.

9.8. CARDIAC FUNCTION

Cardiac Function (ECHO/MUGA) will be performed on the days indicated in Table 1. The overall cardiac function assessment will be reported as "Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant" with respect to relevant abnormalities by the investigator. A shift table comparing the cardiac function assessment over the study visits to baseline measure will be presented.

Left ventricular ejection function (LVEF) will be summarized at each visit and the number of subjects showing a 10% absolute value rise or fall from baseline will be presented. The number of subjects showing a 10% absolute value rise or fall from baseline and number of subjects with LVEF < 50% at any post baseline cycle will also be presented.

Cardiac function will be presented in a listing.

10. INTERIM ANALYSES

No interim analyses will be performed for this study.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The Protocol specified that an interim analysis will be performed when 50% of subjects have completed at least 4 cycles of study drug. Due to the timing of when this interim analysis would have been performed, against the timing of the final analysis, the decision was taken to not perform the interim analysis. As the alpha for the final analysis was not planned to be adjusted due to this interim, no changes to the conduct of the final analysis were made as a result of the cancellation of the interim analysis.

No other deviations from the protocol specified analysis are planned.

12. REFERENCE LIST

1) Lebrecht D, Geist A, Ketelsen U, et al. The 6- maleimidocaproyl hydrazone derivative of doxorubicin (DOXO-EMCH) is superior to free doxorubicin with respect to cardiotoxicity and mitochondrial damage. Int J Cancer. 2006, accepted

2) Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53: 457-481.

13. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.2 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance.

13.2. TABLE, LISTING, AND FIGURE FORMAT

13.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain

subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

  <Sponsor Name> Protocol XXX (INC Research study number xxx)

  Database Build Date :< date>

  Draft/Final Run Date :< date>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date (date output was generated) should appear in the program header

13.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis population should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title, if needed
(<Population Name>)

13.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include "unit" in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a 'All' or 'Total' column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. Table Conventions

- Units will be included where available.

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

Statistical Analysis Plan

- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999 then present as >0.999

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or System Organ Class (SOC) with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

- Missing descriptive statistics or p-values which cannot be estimated should be reported as "-" with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed.

- Where a category with a subheading (such as SOC) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.2. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data will be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates will be printed as recorded on CRF.
- All observed time values must be presented as recorded on CRF.
- Units will be included where available.

13.2.5.3. Figure Conventions

- Unless otherwise specified, for all figures, time will be displayed on the X-axis and endpoint (e.g., overall survival) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, and the listing source (only for table outputs) i.e.,

```
Cross-reference: Listing xx.x
Program: Txxxxxx.sas
```

14. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings and figures. INC Research SOP 03.010.00 and 03.013.00 provide an overview of the development of such SAS programs.

INC Research SOP 03.009.00 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

Refer to the QC plan to review the planned method of QC for each analysis, i.e. double programming, code review, by hand etc.

15. MOCK-UPS

15.1. TABLE MOCK-UPS – ATTACHMENT 1

15.2. FIGURE MOCK-UPS – ATTACHMENT 2

15.3. LISTING MOCK-UPS – ATTACHMENT 3