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CLINICAL STUDY PROTOCOL

Protocol Number	FF1050201US101
Protocol Title	A Phase 1/2a, dose-escalation study of FF-10502-01 for the treatment of advanced solid tumors
Clinical Operations Contact	**Ruth Ann Subach, PharmD, BCPS** Head, Clinical Operations and Project Management FUJIFILM Pharmaceuticals U.S.A., Inc. Phone: (484) 478-3754 Email: rsubach@dsinpharmatics.com
Sponsor / Medical Monitor	**David Wages, MD, PhD** FUJIFILM Pharmaceuticals U.S.A., Inc. One Broadway Cambridge, MA 02142 Phone: (508) 740-7500 Email: david@docwages.com
Original Protocol	November 12, 2014
Amendment #1	October 22, 2015
Amendment #2	March 13, 2017
Amendment #3	July 14, 2017
Amendment #4	March 19, 2018
Amendment #5	December 06, 2018
Amendment #6	August 1, 2019

INVESTIGATOR SIGNATURE PAGE

I have reviewed the above-titled protocol and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of International Council for Harmonisation (ICH) Good Clinical Practice, the Declaration of Helsinki and the applicable U.S. Food and Drug Administration (FDA) regulations.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, case report forms, investigator's brochure, material supplied at investigator meetings, minutes of teleconferences, etc. Such material will only be provided as necessary to site personnel involved in the conduct of the trial, the Institutional Review Board (IRB) or local regulatory authorities.

I will obtain written informed consent from each prospective trial patient or each prospective trial patient's legal representative prior to conducting any protocol-specified procedures. The Informed Consent Document (ICD) used will have the approval of the IRB.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial patients in their medical records. I will accurately complete and submit the electronic case report forms supplied by the Sponsor in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of FUJIFILM Pharmaceuticals U.S.A., Inc. (FPHU), Westat, the IRB or local regulatory authorities. I will ensure that I and my staff are available to meet with representatives of FPHU and Westat during regularly scheduled monitoring visits.

I will notify the Medical Monitor within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to FPHU/Westat as soon as possible, but no later than 5 days following the initial notification.

_____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

2 SYNOPSIS

Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.	**Protocol Number**: FF1050201US101
Name of Study Drug: FF-10502-01	**Protocol Title**: A Phase 1/2a Dose-escalation Study of FF-10502-01 for the Treatment of Advanced Solid Tumors
Name of Active Ingredient: 4'-thio-FAC methane sulfonate	**Phase of Development:** Phase 1/2a

Primary Objective:

- To determine the safety profile, maximum tolerated dose (MTD), dose-limiting toxicities (DLT) and recommended Phase 2 dose (RP2D) in patients who receive FF-10502-01 for treatment of advanced solid tumors

Secondary Objectives:

- To determine overall response rates
- To determine the duration of response and duration of stable disease (SD)
- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)
- To evaluate the pharmacokinetics (PK) of FF-10502
- To evaluate FF-10502 incorporation into whole blood cellular DNA as a pharmacodynamic marker

Methodology:

This is a Phase 1/2a, dose-escalation study of FF-10502-01. A total of up to N=161 patients with advanced solid tumors will be included.

Major selection criteria are: age ≥ 18 years, histologically confirmed solid tumor or lymphoma (lymphoma in Phase 1 only), with documented disease progression following previous therapy. Patients must be ≥ 4 weeks beyond chemotherapy (or ≥ 5 half-lives for targeted agents, whichever is shorter), radiotherapy, major surgery, or other experimental treatments, and recovered from all acute toxicities (≤ Grade 1), have adequate renal and hepatic function, and no known history of significant cardiac disease.

Phase 1:

Following Screening, a total of up to 9 cohorts each will receive FF-10502-01 intravenously (IV) in 500 mL normal saline over a 1-hour period at doses of 8, 12, 18, 27, 40, 60, 90, 135 or 200 mg/m^2 weekly (Day 1, 8, 15) for three weeks, repeated every 28 days (= 1 cycle) until progression of disease.

DLT will be defined as the following drug-related events: Grade 4 thrombocytopenia of any duration; other Grade 4 hematologic toxicity lasting ≥ 7 days; ≥ Grade 3 non-hematologic toxicity (excluding Grade 3 nausea, vomiting or diarrhea that is adequately controlled with supportive care and resolves to ≤ Grade 2 within 48 hours); failure of Grade 3 platelets, absolute neutrophil count (ANC), or hemoglobin (Hb) to recover to Grade ≤ 1 within 4 weeks despite use of platelet and red blood cell (RBC) transfusions and/or growth factors; febrile neutropenia (defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour); Grade 3 or 4 thrombocytopenia of any duration

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associated with bleeding; or other toxicity-related treatment interruption that does not resolve to ≤ Grade 1 by Day 28 when the toxicity has received appropriate medical treatment.

A single-patient dose escalation schema will be followed until the observation of ≥ Grade 2 toxicity. One patient per cohort will be dosed and followed for 28 days through Cycle 1 for DLT. If no ≥ Grade 2 toxicity is seen, the next patient will be enrolled at the next dose level. Dose escalation will proceed in this manner until Grade 2 or greater toxicity is observed in at least one patient per cohort during the first 28 days. At that point, the current dose cohort will be expanded to 3 patients before proceeding in standard 3+3 manner. The dose escalation in subsequent cohorts will proceed in standard 3+3 manner. For all patient cohorts, if 1 of 3 patients per cohort experiences DLT, the cohort will be expanded to 6. If 2 or more of 6 patients per cohort experience DLT, all further dose escalation will stop. If the next lowest dose has only 3 patients, 3 more patients will be treated at that dose to verify it as the MTD. If that dose turns out to be too toxic, then this process will be repeated until the MTD is found through dose de-escalation. If 0 of 3 or ≤ 1 of 6 patients per cohort experience DLT by Day 28 following dosing of FF-10502-01, dose escalation will proceed to the next cohort. The highest dose level below the dose level eliciting DLT in ≥ 2 patients will be declared the MTD. A total of 6 patients will be treated at the MTD. The MTD will be declared the RP2D. No intra-patient dose escalation will be allowed from previous dose levels until at least one patient has completed Cycle 1 at the higher dose level, with no Grade 2 or greater toxicities observed.

Dose level adjustments for DLT will be made. Patients who experience DLT at the first dose level, 8 mg/m^2, will not be dose-reduced, and will be discontinued.

During the study, a Safety Review Committee (SRC) consisting of the actively recruiting investigators, the Medical Monitor, and FPHU, will review data from each cohort on an ongoing basis. Intermediate dose levels may be added if DLT is observed and it is recommended to do so by the SRC. Up to 54 patients are planned for Phase 1.

Phase 2a:

Once 6 patients are treated at the MTD in Phase 1, an additional 4 cohorts will be enrolled. Cohort 10 will enroll any patient with an advanced solid tumor who is otherwise eligible for this study (up to 20 patients). Cohort 11 will enroll patients with cholangiocarcinoma (up to 50 patients). Cohort 12 will enroll patients with carcinoma of the gallbladder (up to 10 patients). Cohort 13 will enroll patients with urothelial carcinoma (up to 27 patients). Eligible patients enrolled in Phase 1 at the MTD may count towards the Phase 2a accrual.

Both phases:

The SRC will review patient data at least quarterly and make recommendations to FPHU regarding the conduct of the trial. Details of the SRC will be outlined in a separate SRC Charter.

Patients in Cohorts 1 to 12 will receive FF-10502-01 on a weekly schedule for 3 weeks (Days 1, 8, and 15), repeated every 28 days. The Phase 2a dose regimen is FF-10502-01 90 mg/m^2, administered on Days 1, 8, and 15 of a 28-day cycle.

Patients in Cohort 13 (urothelial carcinoma) will receive 90 mg/m^2 FF-10502-01 on a weekly schedule for 2 weeks (Days 1 and 8), repeated every 21 days.

For all cohorts, blood samples for safety laboratory, PK, and pharmacodynamic assessments will be collected throughout the study.

Disease assessments, based on computed tomography (CT) and/or magnetic resonance image (MRI), will be obtained at Week 8 and every 8 weeks thereafter until documented

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progression of disease (PD) for Cohorts 1 to 12; and at Week 6 and every 6 weeks thereafter until documented PD for Cohort 13. Patients who demonstrate clinical benefit will be allowed to continue therapy with FF-10502-01 until progression of disease, observation of unacceptable adverse events, intercurrent illness or changes in the patient's condition that prevents further study participation.

Solid tumors will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1)[1].

Number of Patients and Centers:

Phase 1: Up to 54 patients are planned for the dose-escalation phase, with 6 of these patients treated at the MTD.

Phase 2a: Four additional cohorts are planned; Cohort 10 (advanced solid tumors) will enroll up to 20 patients, Cohort 11 (cholangiocarcinoma) will enroll up to 50 patients, Cohort 12 (gallbladder carcinoma) will enroll up to 10 patients, and Cohort 13 (urothelial carcinoma) will enroll up to 27 patients for a total of up to 107 patients.

Entire study: Total N of up to 161 patients.

The study will be conducted at The University of Texas M.D. Anderson Cancer Center, Filip Janku, M.D., Principal Investigator (PI) and Sarah Cannon Research Institute, Denver, CO, Gerald Falchook, M.D., PI. Drs. Janku and Falchook will serve as Co-PIs for the study. Once experience is gained at these institutions. Up to six additional sites may be added to complete study enrollment in a timely manner.

Duration of Study:

Accrual for the Phase 1 dose escalation phase was approximately 24 months. Accrual for the Phase 2a expansion phase is expected to be approximately 21 months, with the last patient followed up every 3 months until death or patient's refusal to participate. The total study duration is expected to be approximately 57 months, through the last patient's last follow-up. The anticipated Phase 2a accrual rate is 3 – 5 patients per month for Cohort 10 and 1-2 patients per month for patients with cholangiocarcinoma, gallbladder carcinoma and urothelial carcinoma (Cohorts 11, 12 and 13).

Inclusion Criteria:

- Males and females ≥ 18 years of age
- Patients must meet one of the following criteria:
    - **Cohorts 1 to 10**: Histologically or cytologically confirmed advanced or metastatic solid tumor or lymphoma (lymphoma in Phase 1 only), that is refractory to standard therapy, relapsed after standard therapy, or for which no standard therapy available that is expected to improve survival by at least three months (Cohort 10 in Phase 2a)

      Or

      Cohort 11 (Phase 2a): Histologically or cytologically confirmed intra- or extra-hepatic cholangiocarcinoma that is refractory to standard therapy, relapsed after standard therapy, or for which no standard therapy available that is expected to improve survival by at least three months

      Or

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- **Cohort 12 (Phase 2a)**: Histologically or cytologically confirmed metastatic and/or unresectable gallbladder carcinoma that has progressed on gemcitabine-based therapy or another systemic therapy and for whom a clinical trial is an appropriate option.

  Or

- **Cohort 13 (Phase 2a)**: Histologically or cytologically confirmed metastatic and/or unresectable urothelial carcinoma that has progressed despite platinum-based therapy. (Note: evidence of progression within 12 months of peri-operative platinum-based therapy will be considered to have met progression criteria.) Patients must also have received a PD-1 or PD-L1 inhibitor and progressed or be ineligible for PD-1/PD-L1 inhibitor therapy or have refused such therapy.

- At least 4 weeks beyond the last chemotherapy (or ≥ 5 half-lives for targeted agents, whichever is shorter), radiotherapy, major surgery or experimental treatment and recovered from all acute toxicities (≤ Grade 1)
- Adequate performance status: Eastern Cooperative Oncology Group (ECOG) ≤ 2 (See APPENDIX A)
- Life expectancy of ≥ 3 months
- Adequate hematologic parameters without ongoing transfusional support:
  - Hemoglobin (Hb) ≥ 9 g/dL
  - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 cells/L
  - Platelets ≥ 100 x 10^9 cells/L
- Prothrombin time and activated partial thromboplastin time < 1.5 × the upper limit of normal (ULN) for the institution. Exceptions are permitted following approval by the Medical Monitor
- Adequate renal and hepatic function:
  - Creatinine ≤ 1.5 x the ULN, or calculated creatinine clearance ≥ 60 mL/minute x 1.73 m^2 per the Cockcroft-Gault formula. Patients enrolled in Cohort 13 (urothelial cancer) must have a calculated creatinine clearance of >30 mL/minute x 1.73 m^2 per the Cockcroft-Gault formula.
  - Total bilirubin ≤ 2 times the ULN unless due to Gilbert's disease
  - ALT and AST ≤ 2.5 times ULN, or < 5 times ULN for patients with liver metastases
- QT interval corrected for rate (QTc) ≤ 480 msec on the electrocardiogram (ECG) obtained at Screening
- Negative serum pregnancy test within 14 days prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months). Sexually active WCBP and male patients must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the

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completion of study treatment.

- Ability to provide written informed consent

Exclusion Criteria:

- Serious cardiac condition within the last 6 months, such as uncontrolled arrhythmia, myocardial infarction, unstable angina or heart disease defined by the New York Heart Association (NYHA) Class III or Class IV (See APPENDIX B)
- Active central nervous system (CNS) malignant disease in patients with a history of CNS malignancy. Patients with stable, previously or currently treated brain metastases are allowed.
- Known positive for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg), or positive hepatitis C antibody. Patients with positive HBsAg, low Hep B DNA, and normal LFTs and patients with low hepatitis C RNA may be considered for enrollment following discussion with the medical monitor.
- Active infection requiring IV antibiotic usage within the last week prior to study treatment
- Any other medical intervention or other condition which, in the opinion of the Principal Investigator, could compromise adherence to study requirements or confound the interpretation of study results
- Pregnant or breast-feeding

Criteria for evaluation:

Safety: Safety will be assessed through the monitoring of AEs, clinical laboratory parameters (hematology, serum chemistry, urinalysis), vital sign measurements, and physical examinations. Adverse events will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded according to the National Cancer Institute Common Terminology Adverse Event (NCI CTCAE) version 4.03.

Efficacy: Efficacy assessments will be determined on the basis of CT and/or MRI scans with best treatment response at any protocol-specified time point classified for solid tumors (RECIST v.1.1), and survival data (PFS and OS).

Pharmacokinetics: Mean plasma concentrations of FF-10502 will be determined at each time point by dose cohort for evaluation of dose-linearity. Because a limited number of plasma concentrations will be determined, full determination of routine PK parameters may not be possible. In addition to mean plasma concentrations, as the data allow, additional PK analyses will be provided (trough levels, $t_{1/2}$, T_{max}, C_{max}, AUC, etc) In Phase 2a, population PK methods will be utilized to characterize the PK profile of FF-10502.

Pharmacodynamics: FF-10502 incorporation into whole blood cellular DNA will be correlated with clinical outcome. In Phase 2a expansion, PK data along with the pharmacodynamic data will be correlated with clinical outcome.

Investigational product:

FF-10502-01 is a pyrimidine nucleoside metabolic inhibitor anti-cancer drug to be administered by IV injection. FF-10502-01 exhibits cell cycle phase-specific activity, and primarily kills cells undergoing DNA synthesis (S-phase), thus blocking the progression of cells through the G1/S-phase boundary.

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FF-10502-01 should be stored under refrigerated conditions at 2 – 8°C. The FF-10502-01 20 mg/mL drug product is manufactured by University of Iowa Pharmaceuticals (Iowa City, IA, USA) and will be provided by the Sponsor, FPHU.	
Reference therapy: None	
Statistical methods: Safety Endpoint Analyses: Safety endpoints for AEs include the following: incidences of all treatment-emergent adverse events (TEAEs) and all serious adverse events (SAEs); number and incidence of TEAEs and SAEs by severity; number and incidence of TEAEs and SAEs by relationship to study drug; number and incidence of all Grade 3 and 4 TEAEs and by severity and relationship to study drug; and discontinuation of patients from the study due to AEs or death. Safety endpoints for AEs, clinical laboratory tests, vital signs, ECG, and physical examination findings will be specified in the statistical analysis plan. Physical examination findings and ECGs will be listed. All other safety data will be summarized using descriptive statistics. Efficacy Endpoint Analyses: Response rates will be summarized using number and percentage of patients with a best response of CR, PR, SD or PD assessed by RECIST v 1.1 across all time points. For duration of response, duration of stable disease, PFS and OS, the Kaplan-Meier product- limit method will be used to estimate the median survival. Patients who do not have disease progression will be censored at the time of last contact. Progression-free survival will be calculated from the date of first treatment to the date of progression or death. Overall survival will be calculated from the date of first treatment to the date of death from any cause; patients who do not experience death will be censored at the time of last contact. SAS Version 9.4 or higher for Windows (SAS Institute, Cary, NC) or higher will be used for all analyses. Pharmacokinetic and Pharmacodynamic Endpoint Analyses: Analysis plans will be described in the written plans provided by the laboratories performing the analyses.	

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT (SGPT)	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate transaminase
AUC	Area under the curve
BM	Bone marrow
BUN	Blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CL	Clearance
cm	Centimeter
C_{max}	Peak concentration
CNS	Central nervous system
CR	Complete response, complete remission
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
dL	Deciliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
ERC	Ethic Review Committee
FAC	Arabinofuroanosyl cytosine
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FPHU	FUJIFILM Pharmaceuticals, U.S.A., Inc.
g	Gram
GALT	Gut-associated lymphoid tissue

Abbreviation	Definition
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
G1/S	Gap 1/S phase interface
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IC_{50}	Concentration producing 50% inhibition
ICD	Informed consent document
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
INR	International normalized ratio (of prothrombin time)
IWG	International Working Group
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
M	Molar
m^2	Meters squared
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
µ	Micro
mg	Milligram
mL	Milliliter
min	Minute
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
n	Nano
NCI	National Cancer Institute
NYHA	New York Heart Association

Abbreviation	Definition
OR	Objective response
OS	Overall survival
p	Probability
PBS	Phosphate buffered saline
PD	Progression of disease
PET	Positron emission tomography
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PR	Partial response, partial remission
PT	Prothrombin time
QTc	QT interval corrected for rate
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Stable disease
SRC	Safety Review Committee
T1/2	Half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to peak concentration
ULN	Upper limit of normal
WCBP	Woman of child-bearing potential

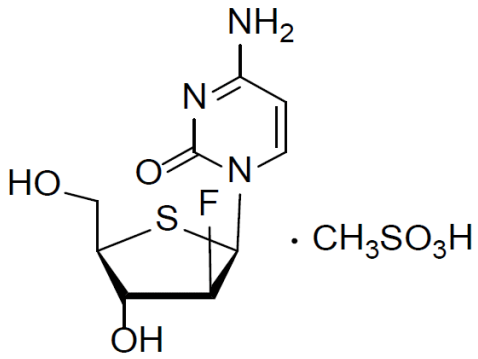
4 INTRODUCTION

4.1 FF-10502-01 Background

FF-10502, 4-amino-1-[(2R,3S,4S,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl) tetrahydrothiophen-2-yl]pyrimidin-2(1H)-one, or 4'-thio-FAC, is a pyrimidine nucleoside antimetabolite anticancer agent. Pyrimidine antimetabolites exert cell cycle phase-specific activity by killing cells undergoing DNA synthesis (S-phase) and blocking the progression of cells through the G1/S-phase boundary.

4'-thio-FAC was originally synthesized by Yamasa Corporation (Chiba, Japan) and licensed to Schering AG (Berlin, Germany) for development. The synthetic process was improved by Schering (reference code name ZK 820973). FUJIFILM acquired the compound in 2011, improved the synthetic process further, including solubility, and is now developing the methanesulfonate salt as FF-10502-01. The chemical structure of FF-10502-01 is depicted in Figure 1.

Figure 1. Chemical Structure of FF-10502-01



ZK 820973 is the compound designation for studies previously conducted with FF-10502 (free base) by Schering AG. FF-10502-01 (methanesulfonate salt) is the test article used in all studies conducted under the direction of FUJIFILM.

4.2 ZK 820973 Preclinical Summary

4.2.1 ZK 820973 Preclinical Pharmacokinetics, Distribution, Metabolism, Excretion

Schering conducted nonclinical pharmacokinetic (PK), distribution, metabolism and excretion studies with ZK 820973. Following intravenous (IV) administration, these studies demonstrated that ZK 820973 has a similar profile to other pyrimidine nucleoside analogues, including gemcitabine.[2,3]

The pharmacokinetics following single, bolus IV doses, 4 mg/kg in the mouse indicate a similar pharmacokinetic profile to gemcitabine. The half-life ($t_{1/2}$) was 0.44 hours and area under the curve (AUC) was 1.4 µg*hr/mL, versus 0.14 hours and 0.7 µg*hr/mL for gemcitabine.

In rats, single, bolus IV doses of 1, 5 or 20 mg/kg ZK 820973 or two doses of 2.5 mg/kg administered 1 hour apart, demonstrated dose-dependent systemic exposure in both sexes, however, 2 times administration of ZK 820973 show no difference in AUC, C_{max} and other PK parameters compared to single administration of the same total dose. Different PK profiles were noted in females and males; higher C_{max}, greater AUC and longer $t_{1/2}$ noted in females versus males, resulting in overall lower exposure in males.

In dogs, similar kinetics were noted between females and males following a single, bolus IV dose of 5 mg/kg; $t_{1/2}$ was 16.6 hours, AUC was 21.5 µg*hr/mL, clearance (CL) was 4.1 mL/min/kg; these values represent higher exposure in dogs relative to rats.

ZK 820973 exhibited low protein binding following IV administration.

Distribution of ZK 820973 in male and female rats following a single, bolus IV dose of 5 mg/kg 14C-ZK 820973 indicated highest concentrations in the kidney. No long-lasting retention was noted in any organ or tissue. ZK 820973 passes through the blood-brain barrier, the placental barrier, and is expected to be secreted into milk. Elimination was mainly via the kidney.

Metabolism was mainly by deamination in the mouse, dog, monkey and human, and less so in the rat. No metabolism of ZK 820973 was observed following incubation with human liver microsomes and isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4; therefore, there is no significant metabolism by the cytochrome P450 enzyme system. Additionally, no interaction with CYP P450 enzymes was noted. Based on in

vitro inhibition studies, it was not expected that ZK 820973 would cause metabolic interactions when co-administered with drugs known to be cleared predominantly by CYP-dependent metabolism. Therefore, there is little potential for drug-drug interactions.

4.2.2 ZK 820973 Preclinical Safety Pharmacology

The cardiac effects of ZK 820973 were evaluated in vitro in guinea pig atria.[3] Concentrations of ZK 820973 from 1 – 100 µmol/L were evaluated. The highest concentration (100 µmol/L) represented a ≥ 300-fold higher concentration than that needed to produce anti-proliferative, cytotoxic effects in MCL, pancreatic, ovarian, lung, colon, and prostate tumor cell lines. ZK 0820973 did not provoke significant effects on rate or force of contractions of isolated guinea pig atria in comparison to vehicle control.

4.2.3 ZK 820973 Genetic Toxicology

ZK 820973 was tested in the Ames Salmonella reverse mutation assay using strains TA98, TA100, TA1535, TA1537, and TA102.[4] The compound was tested in both the presence and absence of S9 metabolic activation. ZK 820973 was found not to be mutagenic in the Ames strains tested either in the absence or presence of S9 metabolic activation.

4.3 FF-10502-01 Preclinical Studies

4.3.1 FF-10502-01 In Vitro Anti-tumor Activity

FF-10502-01 has demonstrated in vitro activity against pancreatic (BxPC-3, Capan-1, MIA PaCa-2, SUIT-2), colon (HCT116), lung (NCI-H460), ovarian (SK-OV-3), prostate (LNCaP.FGC) and mantle cell lymphoma (MCL) (Jeko-1) cell lines. The growth inhibition is shown in Table 1, as the mean of 3 experiments +/- SD. FF-10502-01 demonstrated growth inhibition activity with concentrations producing 50% inhibition (IC_{50}s) of 30 – 330 nM; however the activity was 1.5- to15-fold lower than gemcitabine.[5,6,7]

Table 1. Growth Inhibition of FF-10502-01 and Gemcitabine in Human Tumor Cell Lines

Cell Origin	Cell Line	FF-10502-01 (IC_{50} nmol/L)	Gemcitabine (IC_{50} nmol/L)
Pancreas	BxPC-3	59.9 ± 11.5	17.7 ± 4.9
Pancreas	SUIT-2	39.6 ± 0.7	3.7 ± 0.1
Pancreas	Capan-1	68.2 ± 2.7	22.4 ± 1.6
Pancreas	MIA PaCa-2	331.4 ± 233.8	27.5 ± 9.8
Colon	HCT116	30.0 ± 3.4	6.0 ± 0.3
Lung	NCI-H460	79.5 ± 31.3	5.3 ± 3.1
Ovary	SK-OV-3	65.5 ± 13.1	45.6 ± 4.0
Prostate	LNCaP.FGC	73.0 ± 19.2	14.6 ± 6.3
Breast	MDA-MB231	> 10000	603.1 ± 291.0
MCL	Jeko-1	11.6 ± 7.5	2.7 ± 0.5

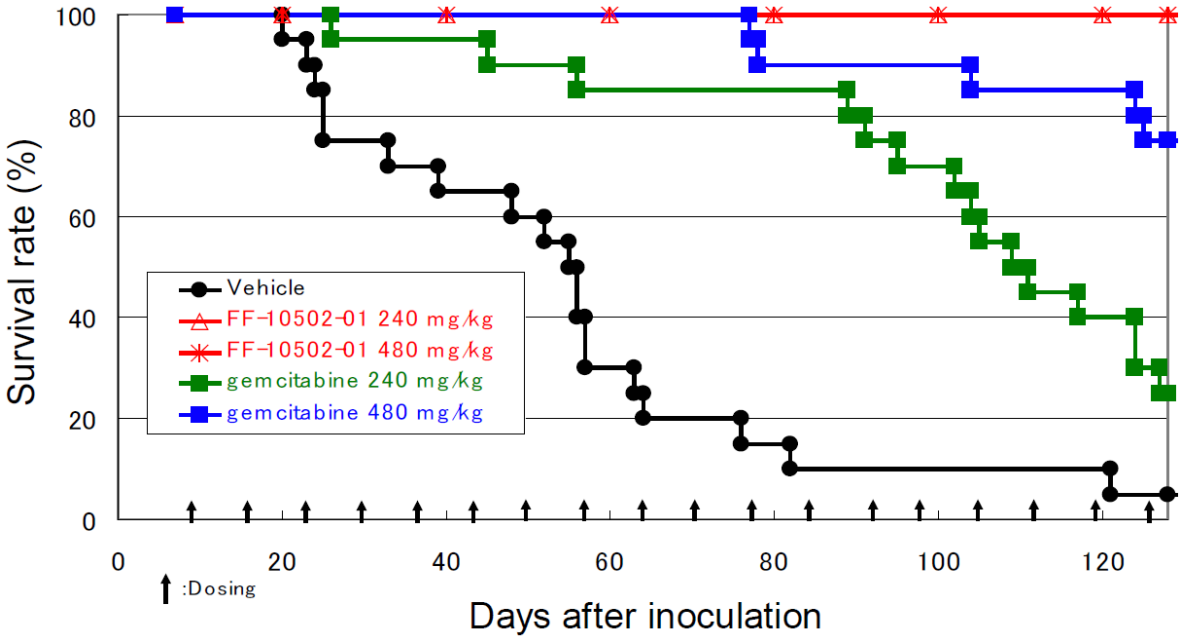
Abbreviations: IC_{50} = concentration producing 50% inhibition, MCL = mantle cell lymphoma

4.3.2 FF-10502-01 In Vivo Anti-tumor Activity

FF-10502-01 demonstrated in vivo activity in pancreatic xenograft models (SUIT-2, Capan-1) at doses achievable clinically.

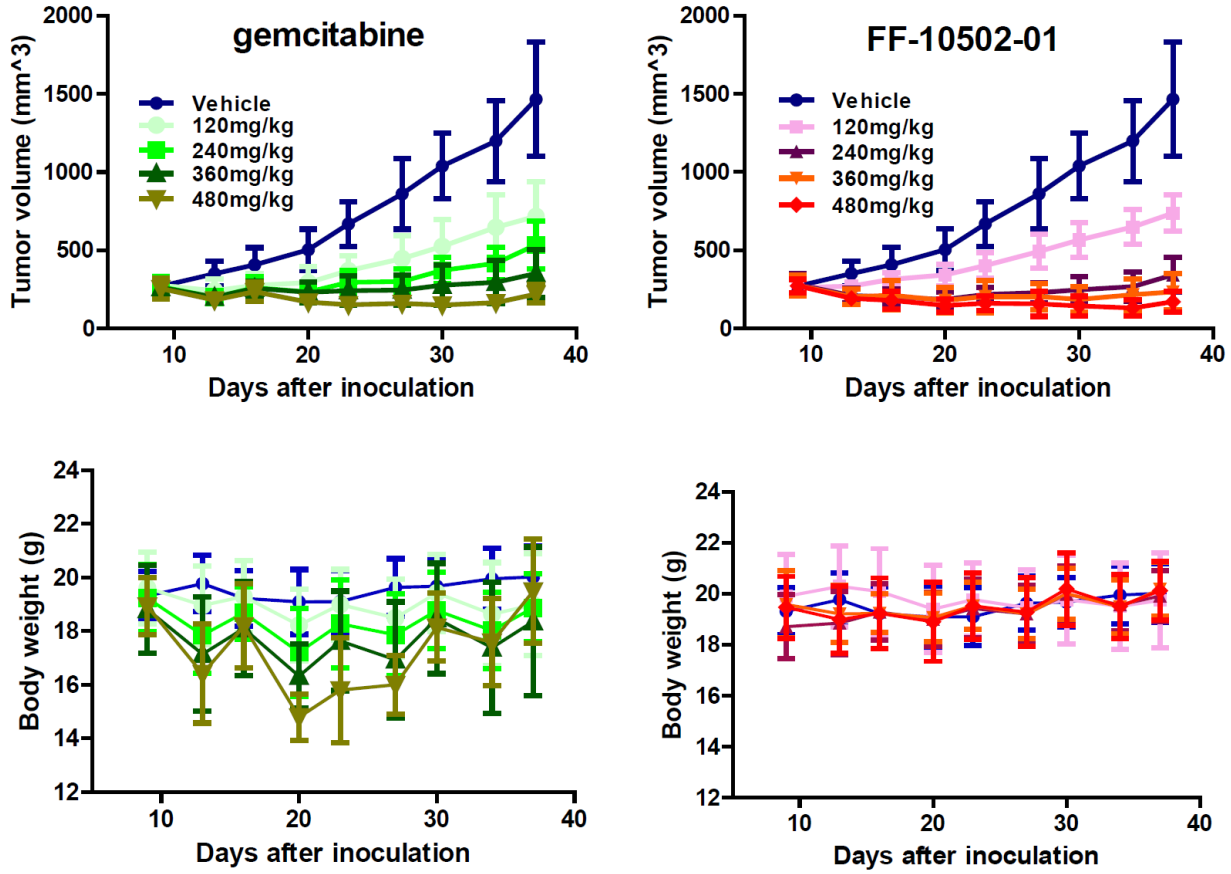
A human pancreatic cancer cell line (SUIT-2) was transplanted orthotopically into nude mice, and FF-10502-01 or gemcitabine was administered at 240 or 480 mg/kg once a week beginning on Day 7 after transplantation and continuing for 18 weeks.[8] Each group consisted of N=20 animals/group. The animals were followed up for 128 days after transplantation. Median survival in the vehicle control and 240 mg/kg gemcitabine groups was 55 and 110 days, respectively (p=0.0002). Median survival was not reached for the 480 mg/kg gemcitabine group or either the 240 or 480 mg/kg FF-10502-01 groups. The survival rate was 5%, 25%, 75% for the vehicle, 240 and 480 mg/kg gemcitabine groups (p<0.0001 versus vehicle), and 100% for the 240 and 480 mg/kg FF-10502-01 groups (p<0.0001 versus gemcitabine groups), respectively (Figure 2).

Figure 2. Survival in SUIT-2 Orthotopic Pancreatic Xenograft Model Following Treatment with FF-10502-01 or Gemcitabine



A cultured human pancreatic cancer cell line, Capan-1 was subcutaneously transplanted into the right flank of nude mice. Seven days after transplantation, FF-10502-01 or gemcitabine was administered at 120, 240 or 480 mg/kg once a week for 4 weeks.[9] Tumor growth inhibitory effects of the test substance were evaluated for 27 days after starting treatment. Both FF-10502-01 and gemcitabine demonstrated statistically significant tumor growth suppression versus vehicle control; FF-10502-01 demonstrated tumor growth suppression with less effect on body weight than gemcitabine (Figure 3). Each graph represents 3 experiments ±SD.

Figure 3. Tumor Growth Suppression and Body Weight in Capan-1 Subcutaneous Xenograft Model Following Treatment with FF-10502-01 or Gemcitabine



4.3.3 FF-10502-01 Inhibition of DNA Synthesis

The effects of FF-10502-01 or gemcitabine on DNA synthesis in human pancreatic cancer-derived cell lines (Capan-1) were evaluated for inhibition of DNA synthesis 50% (IC_{50}).[10] The mean IC_{50} (nmol/L) was 27.8 for FF-10502-01 and 29.6 for gemcitabine, indicating comparable inhibition of DNA synthesis in a human pancreatic cancer cell line.

Additionally, FF-10502-01 demonstrated higher inhibitory potency than gemcitabine in an enzyme assay of DNA replication.[11] The IC_{50}s (μM) of DNA synthesis were 23 and 547 for FF-10502-01 and gemcitabine, respectively, demonstrating 23-fold higher inhibition than gemcitabine by DNA α-polymerase-mediated synthesis.

4.3.4 Preclinical Pharmacokinetics, Protein Binding, Liver Microsome Stability

4.3.4.1 Pharmacokinetics

Rat: The objective of the study was to determine the toxicokinetic profile when FF-10502-01 was administered once weekly for three weeks (Days 1, 8 and 15) by intravenous infusion over a period of 1 hour to Sprague Dawley rats in a toxicology study conducted under Good Laboratory Practice (GLP) conditions described in Section 4.4.1.2 below.[12]

The test and control/vehicle items were administered to groups of rats on 3 occasions (Days 1, 8 and 15) by a 1-hour IV infusion at doses of 0, 100, 250 and 500 mg/kg (expressed as FF-10502 free base). Blood samples were collected from subsets of animals on Days 1 and 15

at 8 time points relative to treatment. A total of 3 animals per sex were evaluated for toxicokinetics from the control group; a total of 6 animals per sex were evaluated for toxicokinetics from the high dose group.

FF-10502 was not detected in any of the samples collected from the Control animals on Days 1 and 15. Similarly, FF-10502 was not detected in any of the pre-dose samples collected from the treated animals (100, 250 and 500 mg/kg dose groups) on Days 1 and 15.

At doses of 100, 250 and 500 mg/kg/dose, exposure (based on C_{max} and $AUC_{0\text{-}Tlast}$ /AUC_{INF} values) to FF-10502 increased in a generally dose proportional manner for C_{max} and AUC on both Day 1 and Day 15. C_{max} was reached at 5 minutes post end of infusion for all animals. After reaching T_{max}, the FF-10502 plasma concentrations declined rapidly at a mean estimated $t_{1/2}$ value ranging from 0.63 to 0.86 hours on Day 1 and from 0.75 to 0.90 hours on Day 15, at a dose of 100 mg/kg. On Day 15, the mean $AUC_{0\text{-}Tlast}$ was 211.5 and 200 hr*µg/mL for males and females, respectively, corresponding to a mean C_{max} of 139.9 and 126.2 µg/mL, respectively, at a dose of 250 mg/kg.

FF-10502 levels detected in all treated group samples collected at 12 hours post dose on Days 1 and 15 suggests that FF-10502-01 is eliminated within 12 hours of administration. There were no noteworthy sex-related differences in any of the measured toxicokinetic parameters. The once weekly IV infusion of FF-10502-01 over a period of 1 hour for 3 weeks did not result in any accumulation in rats.

Dog: The objective of the study was to determine the toxicokinetic profile when FF-10502-01 was administered once weekly for three weeks (Days 1, 8 and 15) by IV infusion over a period of 1 hour to Beagle dogs in a GLP toxicology study described in Section 4.4.2.2 below.[13] Blood samples for toxicokinetic profiling were collected from the Main animals on Days 1 and 15 (Day 8 for high-dose animals euthanized early) at a series of time points relative to treatment. A total of 1 animal per sex per group was evaluated for toxicokinetics at each respective dose level.

FF-10502 was not detected in any of the samples collected from the control animals on Days 1 and 15. Similarly, FF-10502 was not detected in any of the pre-dose samples collected from the treated animals on Days 1 and 8/15.

At doses of 2.5, 5 and 10 mg/kg/dose (expressed as FF-10502 free base), exposure (based on C_{max} and $AUC_{0\text{-}Tlast}$/AUC_{INF} values) increased in a generally dose proportional manner for C_{max} and AUC on both Day 1 and Day 8/15, excepted for AUC in the high-dose males which increased in a slightly less than dose proportional manner on Day 8. C_{max} was reached at 5 minutes post end of infusion for all animals. After reaching T_{max}, the FF-10502 plasma concentrations gradually declined at a mean estimated $t_{1/2}$ value ranging from 2.78 to 3.95 hours on Day 1, and from 2.58 to 4.74 hours on Day 8/15. On Day 15, the $AUC_{0\text{-}Tlast}$ was 16.6 and 13.8 hr*µg/mL for males and females, respectively, corresponding to a C_{max} of 3.38 and 2.85 µg/mL, respectively.

FF-10502 levels noted in all of low-, mid- and high-dose samples collected at 24 hours post dose on Days 1 and 8/15 suggest that FF-10502-01 is eliminated within 24 hours of administration. There were no noteworthy sex-related differences in any of the measured toxicokinetic parameters. Once weekly IV infusion of FF-10502-01 over a period of 1 hour for up to 3 weeks did not result in an accumulation in dogs.

4.3.4.2 Protein Binding

The plasma protein binding of FF-10502-01 was evaluated by means of equilibrium dialysis in plasma against phosphate buffered saline (PBS) at physiological conditions (37°C and pH 7.4),

at concentrations of 0, 0.137, 1.37, 4.13, 13.7, 41.3, 137 µM in rat, dog, and human plasma.[14] Time to reach equilibrium was determined to be 2 hours. FF-10502-01 was found to be stable in rat, dog and human plasma. Negligible plasma protein binding for FF-10502-01 was observed across all concentrations evaluated in rat, dog, and human plasma. The results of this study are consistent with the results obtained from the protein binding study previously conducted with ZK 820973.

4.3.4.3 Liver Microsome Stability

The metabolic stability of FF-10502-01 was evaluated in human, rat, mouse and dog liver microsomes in order to predict in vivo metabolism, to determine the optimal species for assessment of the compound in in vivo animal studies.[15] FF-10502-01 was found to be very stable metabolically in all tested species (mean $t_{1/2}$ > 180 minutes), with intrinsic clearances of 9, 6, 11 and 7 µL/min/mg in human, rat, mouse and dog liver microsomes, respectively. The observed differences in the metabolism rates were determined to be within experimental variability and did not indicate a difference between species with respect to FF-10502-01 metabolism.

4.4 FF-10502-01 Toxicology

4.4.1 Dose Range-Finding and Repeat-Dose Toxicity Studies in Rats

4.4.1.1 Dose Range-Finding in Rats

This dose range-finding study was conducted in 2 parts. Phase 1 (dose-escalation) was conducted to determine the MTD of FF-10502-01 when administered once by intravenous infusion over a period of 1 hour to Sprague Dawley rats. Phase 2 (repeat-dose) was conducted to determine the toxicity of FF-10502-01 when administered weekly for 2 weeks (Days 1 and 8) by intravenous infusion over a period of 1 hour to Sprague Dawley rats.[16]

Phase 1 (Dose-Escalation): This portion of the study was conducted to determine the MTD of FF-10502-01 when administered once by intravenous infusion over a period of 1 hour to Sprague Dawley rats. Doses of 0, 200, 400 and 100 mg/kg (FF-10502 free base) were administered to 2 animals per sex per group. An observation period of 4 days was allowed between successive dose levels. Parameters monitored included mortality, clinical observations, body weights, and food consumption; hematology, coagulation and clinical chemistry parameters were evaluated on Day 8. At termination, all animals were euthanized and subjected to a gross necropsy examination. Organ weights were measured on selected organs and a complete list of tissues, including gross lesions, were retained.

Slight increases in platelets and reticulocyte counts were noted at doses up to 400 mg/kg. At 1000 mg/kg, clinical signs, body weight loss (males only), decreases in food intake (male only), were noted, as well as increases in white blood cells and neutrophils in the animals of both sexes. The MTD was determined to be 400 mg/kg.

Phase 2 (Repeat-Dose): This portion of the study was conducted to determine the toxicity profile when FF-10502-01 was administered weekly for 2 weeks (Days 1 and 8) by IV infusion over a period of 1 hour to Sprague Dawley rats (5 males and 5 females) at 750 mg/kg, an intermediate dose to the 400 and 1000 mg/kg doses evaluated above as single doses. Parameters monitored included mortality, clinical observations, body weights, and food consumption; hematology, coagulation, clinical chemistry and urinalysis parameters were evaluated on Day 15. At termination, all animals were euthanized and subjected to a gross necropsy examination. Organ weights were measured on selected organs and a complete list of tissues, including gross lesions, were retained and prepared for microscopic evaluation.

The weekly 1-hour intravenous infusion of FF-10502-01 for 2 weeks at a dose of 750 mg/kg resulted in mortality (two females), clinical signs, decreases in body weights and food consumption and increases in platelets, reticulocytes, white blood cells, neutrophils and monocytes. Macroscopically, test item related macroscopic observations in the spleen (enlargement), testes (small/soft and dark discoloration), thymus (small) and several lymph nodes (enlargement) were noted. Microscopically, test item related findings in the spleen (decreased cellularity in the white pulp and extramedullary hematopoiesis in the red pulp), testes (degeneration/atrophy) thymus (decreased cellularity) several lymph nodes (increased cellularity) and femoral bone marrow (enostosis) were noted.

Therefore, the MTD in the dose range finding study in the rat was determined to be 400 mg/kg.

4.4.1.2 Repeat-Dose in Rats

The objective of this GLP study was to determine the toxicity and toxicokinetic profile of FF-10502-01 when administered once weekly for three weeks (Days 1, 8 and 15) by IV infusion over a period of 1 hour to Sprague Dawley rats and to evaluate the persistence, delayed onset or reversibility of any test item-related effects following a 14-day recovery period.[12] The toxicokinetic results are summarized in Section 4.3.4.1 above.

The test and control/vehicle items were administered to groups of rats on 3 occasions (Days 1, 8 and 15) by a 1-hour intravenous infusion at doses of 0, 100, 250 and 500 mg/kg (expressed as FF-10502 free base). A total of 10 animals per sex per group were included in the main study, and 5 animals per sex per group in the recovery study (control and high dose only).

Parameters monitored during this study included mortality, clinical observations, body weights, food consumption and ophthalmology; hematology, coagulation, clinical chemistry and urinalysis parameters were evaluated on Day 22 (Main animals) and on Day 29 (Recovery animals). At termination (Day 22; Main animals; Day 29, Recovery animals), all animals were euthanized and subjected to a gross necropsy examination. Organ weights were measured on selected organs and a selected list of tissues, including gross lesions, were retained and prepared for microscopic evaluation.

At a dose of 100 mg/kg/dose, IV infusion of FF-10502-01 resulted in no mortalities, no adverse clinical signs, no changes in body weights, food consumption, coagulation, serum chemistry or urinalysis parameters. In addition, there were no macroscopic or microscopic findings. Increases in reticulocyte count were noted, as was a decrease in lymphocyte count, testicular and thymic weights.

At a dose of 250 mg/kg/dose, no mortalities were noted, nor were changes in coagulation or urinalysis parameters seen. Clinical signs, consisting mainly of inflammatory changes (suggestive of systemic septicemia) in the skin and subcutis (confirmed microscopically) and decreases in body weight gain (in males only) and food consumption were noted. Changes in hematology and clinical chemistry parameters were noted, as were decreases in testicular and thymic weights. Macroscopically, enlargement of the spleen and thickening of the skin and subcutis were noted. Microscopic changes included myeloid hypercellularity (with concurrent decrease in erythroid precursor cells) in the bone marrow (femur and sternum), decreased cellularity of thymus and spleen (white pulp), increased extramedullary hematopoiesis in spleen (red pulp), seminiferous tubular degeneration/atrophy (associated with oligospermia/aspermia) of the testes/epididymides.

At a dose of 500 mg/kg/dose, no changes in coagulation or urinalysis parameters were noted. However, 1 male and 1 female rat were pre-terminally euthanized following the third dose due to poor condition. In these 2 pre-terminally euthanized animals, as well as in the animals surviving to termination, clinical signs were noted, consisting mainly of inflammatory changes (suggestive

of systemic septicemia) in the skin and subcutis (confirmed microscopically), hunched posture, decreased activity, thin body condition, reduced grooming activities (fur dull, ungroomed, matted), ptosis, dehydration and sensitivity to touch, and decreases in body weight gain and food consumption. Changes in hematology and clinical chemistry parameters were noted, as well as decreases in testicular and thymic weights and increases in splenic weight. Macroscopic observations were noted in the testes/epididymides (small and/or dark discoloration/soft), spleen (enlargement and/or pale area/material/adhesion), thymus (small), skin and subcutis (thickening/dark discoloration) and adrenals (dark/pale area). Microscopic changes included myeloid hypercellularity (with concurrent decrease in erythroid precursor cells) in the bone marrow (femur and sternum), decreased cellularity of thymus and spleen (white pulp), increased extramedullary hematopoiesis in spleen (red pulp), seminiferous tubular degeneration/atrophy (associated with oligospermia/aspermia) of the testes/epididymides.

During the Recovery period (Day 22 to 29 following the last FF-10502-01 dose on Day 15), the majority of the clinical signs were reversible and were no longer seen beyond Day 22, except for reddening and swelling of the pinnae, which was still observed in all the Recovery females, and swelling of the left hind paw, in one male. Body weight gain and food consumption in high dose animals were comparable to controls; therefore, the effect on these parameters was considered reversible. In addition, changes in hematology and clinical chemistry parameters were noted, as well as decreases in testicular weight and increases in thymic and splenic weights. Macroscopic observations were still present in the testes/epididymides (small and/or soft), spleen (enlargement and raised area/adhesion) and skin and subcutis (thickening/dark discoloration). Microscopically, decreased cellularity (lymphoid depletion) in the thymus was no longer present, suggesting complete reversibility of the finding in the animals treated at 500 mg/kg/dose. Lower incidence and severity of myeloid hypercellularity was noted in the bone marrow, as was lower severity of decreased cellularity, and increased extramedullary hematopoiesis in the spleen, suggesting a partial to complete reversibility of the finding in the animals treated at 500 mg/kg/dose. The testes/epididymides findings were still present in all the animals treated at 500 mg/kg/dose. The testicular tubular degeneration/atrophy with oligospermia aspermia observed was not considered reversible. In addition, subcutaneous inflammation (skin and subcutis), suggestive of systemic septicemia, was still observed in one male and all of the female animals treated at 500 mg/kg/dose.

Therefore, the MTD for FF-10502-01 when administered once weekly for 3 weeks in rats was determined to be 250 mg/kg.

4.4.2 Dose Range-Finding and Repeat-Dose Toxicity Studies in Dogs

4.4.2.1 Dose Range-Finding in Dogs

This dose range-finding study was conducted in 2 parts. Phase 1 (dose-escalation) was conducted to determine the MTD of FF-10502-01 when administered once by IV infusion over a period of 1 hour to Beagle dogs. Phase 2 (repeat-dose) was conducted to determine the toxicity of FF-10502-01 when administered weekly for 2 weeks (Days 1 and 8) by intravenous infusion over a period of 1 hour to Beagle dogs.[17]

Phase 1 (Dose-Escalation): This portion of the study was conducted to determine the MTD of FF-10502-01 was administered once by IV infusion over a period of 1 hours to Beagle dogs. Doses of 0, 5, 10 and 25 mg/kg (FF-10502 free base) were administered to 1 animal per sex per group. An observation period of 4 days was allowed between successive dose levels. Parameters monitored during this study included mortality, clinical observations, body weights, and food consumption; hematology parameters were evaluated on Day 8. At termination, all animals were euthanized and subjected to a gross necropsy examination. Organ weights were

measured on selected organs and a complete list of tissues, including gross lesions, were retained.

A dose of 5 mg/kg resulted in mild clinical signs (liquid/loose feces in 2 animals) as well as hematological changes consisting mainly of slight neutropenia. At a dose of 10 mg/kg, decreased food consumption was noted, as well as hematological changes, consisting mainly of moderate neutropenia and slight decreases in platelets, monocytes, eosinophils and basophils.

A single dose of 25 mg/kg resulted in the following clinical signs: decreased activity, liquid feces, body weight loss, decreased food consumption and hematological changes consisting mainly of moderate neutropenia, slight lymphopenia and slight decreases in reticulocytes, platelets, monocytes, eosinophils and basophils. In the male, macroscopic changes were noted in the last infusion site, mesenteric and pancreatic lymph nodes. In the female, macroscopic changes were noted in the last infusion site, the digestive tract contents, colon, and pancreatic lymph node. The MTD was determined to be 10 mg/kg.

Phase 2 (Repeat-Dose): The portion of the study was conducted to determine the toxicity profile when FF-10502-01 was administered weekly for 2 weeks (Days 1 and 8) by IV infusion over a period of 1 hour to Beagle dogs (2 males and 2 females) at 15 mg/kg, an intermediate dose to the 10 and 25 mg/kg doses evaluated above as single doses. All animals were to be observed for a period of 7 days following completion of dosing and then euthanized and subjected to a necropsy examination on Day 15. However, one female dog was found dead, while the remaining three were pre-terminally euthanized on Day 12 (4 days following the second dose), due to poor and deteriorating clinical condition.

Parameters monitored during this study included mortality, clinical observations, body weights, and food consumption; hematology, coagulation, clinical chemistry and urinalysis parameters were evaluated on Days 8 and 12. At termination, all animals were euthanized and subjected to a gross necropsy examination. A complete list of tissues, including gross lesions, were retained and prepared for microscopic evaluation.

The weekly IV infusion of FF-10502-01 for 2 weeks at a dose of 15 mg/kg resulted in severe clinical signs, marked body weight loss, severe decreases in food consumption, as well as changes to a number of hematology and clinical chemistry parameters and led to the death of one female and the pre-terminal euthanasia of the remaining 3 animals on Day 12 of the study.

Microscopic changes observed in the found death and pre-terminally euthanized animals were similar and consisted mainly of decreased hematopoiesis of the femoral bone marrow, congestion and/or congestion/hemorrhage in the digestive tract (duodenum, jejunum, ileum colon, cecum and/or rectum), cryptal necrosis (duodenum, jejunum, colon, cecum and/or rectum), decreased cellularity of gut-associated lymphoid tissue (GALT), mandibular lymph node and/or thymus, congestion of the mandibular lymph node and/or mixed cell infiltrate/perivascular hemorrhage at the last infusion site.

Therefore, the MTD in the dose range-finding study in the dog was determined to be 10 mg/kg.

4.4.2.2 Repeat-Dose in Dogs

The objective of this GLP study was to determine the toxicity and toxicokinetic profile of FF-10502-01 when administered once weekly for 3 weeks (Days 1, 8 and 15) by IV infusion over a period of 1 hour to Beagle dogs and to evaluate the persistence, delayed onset or reversibility of any test-item related effects following a 14-day recovery period.[13] The toxicokinetic results are summarized in Section 4.3.4.1 above.

The objective of the study was to determine the toxicity and toxicokinetic profile of the test item, FF-10502-01, when administered once weekly for three weeks (Days 1, 8 and 15) by

intravenous infusion over a period of 1 hour to Beagle dogs and to evaluate the persistence, delayed onset or reversibility of any test item-related effects following a 14-day recovery period.

The test and control/vehicle items were administered to groups of dogs on 3 occasions (Days 1, 8 and 15) by a 1-hour IV infusion at doses of 0, 2.5, 5 and 10 mg/kg (expressed as FF-10502 free base). A total of 3 animals per sex per group were included in the main study, and 2 animals per sex per group in the recovery study (control and high dose only).

Parameters monitored during this study included mortality, clinical observations, body weights, food consumption, ophthalmology, blood pressure and electrocardiograms; hematology, coagulation, clinical chemistry and urinalysis parameters were evaluated on Day 22. Following the third dose on Day 15, the Group control and low dose Main animals were observed for a period of 7-days and then euthanized and subjected to a necropsy examination on Day 22. The control group Recovery animals were to be observed for 14 days following completion of the last dose (Day 15) and then euthanized and subjected to a necropsy examination on Day 29, however, due to the pre-terminal euthanasia of all high-dose Recovery animals, the control group Recovery animals were euthanized and subjected to a necropsy examination on Day 22 along with the Main animals. The mid- and high-dose Main animals were to be observed for a period of 7 days following their third dose (Day 15) and then euthanized and subjected to a necropsy examination on Day 22, while the high-dose Recovery animals were to be observed for 14 days following completion of the last dose (Day 15) and then euthanized and subjected to a necropsy examination on Day 29. However, due to the pre-terminal euthanasia of two high-dose Recovery males on Days 8 and 9, respectively, following 1 or 2 doses, the high-dose Main animals and the remaining high-dose Recovery females were euthanized on Day 10 (2 days following administration of the second dose). The high-dose Main animals were reassigned as Recovery animals, dosed on Day 8 and were to be euthanized on Day 22 (2 weeks following administration of the second dose). However, in view of their poor clinical condition, all of the remaining high-dose animals were euthanized between Days 13 and 15 (after receiving 2 doses only), while all the animals from the mid-dose group were euthanized between Days 14 and 17 (after receiving 2 to 3 doses).

At a dose of 2.5 mg/kg/dose, FF-10502-01 resulted in no mortalities, no changes in ophthalmology, blood pressure, electrocardiography, coagulation or urinalysis parameters. In addition, there were no macroscopic or microscopic findings. Clinical signs were noted in a small number of animals, marginal body weight loss and decreases in food consumption, decreases in white blood cells (mainly neutrophils, lymphocytes and/or eosinophils), as well as decreases in thymic weights. The decreased in the weight of the thymus were minor and were not associated with any macroscopic or microscopic correlates.

At a dose of 5 mg/kg/dose, no changes in ophthalmology, blood pressure, electrocardiography, coagulation or urinalysis parameters were noted, and no macroscopic findings were observed. Adverse clinical signs, body weight loss and decreased food consumption (males only) was noted, which led to the pre-terminal euthanasia of all animals between Days 14 and 17 following the administration of 2 to 3 doses of FF-10502-01. Changes in hematology and clinical chemistry parameters were noted and decreased thymic and testicular weights. Microscopic changes included decreased cellularity (lymphoid depletion) in the thymus and GALT, hypocellularity of the bone marrow (sternum and/or femur), atrophy of the testicular seminiferous tubular epithelium and pulmonary inflammation (suppurative/hemorrhagic bronchioloalveolar and/or granulomatous inflammation) mostly associated with a secondary bacterial infection.

At a dose of 10 mg/kg/dose, no changes in ophthalmology, blood pressure, electrocardiography or urinalysis parameters were noted. Adverse clinical signs, body weight loss and decreased in

food consumption were observed, which led to the death or pre-terminal euthanasia of all animals between Days 8 and 15 of the study following the administration of 1 to 2 doses of FF-10502-01. Changes in hematology, coagulation and clinical chemistry parameters, were noted, as well as decreases in thymic and testicular weights. Macroscopic changes included mottling or dark area/discoloration of the lungs, presence of a mass in the ventricular chamber of the heart, raised area in the atrioventricular valve of the heart and small thymus. Microscopic changes included decreased cellularity (lymphoid depletion) in the thymus and GALT, hypocellularity of the bone marrow (sternum and/or femur), atrophy of the testicular seminiferous tubular epithelium, pulmonary inflammation (suppurative/hemorrhagic bronchioloalveolar and/or granulomatous inflammation) mostly associated with secondary bacterial infection and mural thrombosis or blood clot formation in the heart.

The combined effects of immunosuppression and/or secondary bacterial sepsis were considered to be the major cause of the death or poor clinical condition that led to the premature euthanasia of the 5 and 10 mg/kg/dose animals and are not unexpected findings for cytotoxic agents given at high doses.

Therefore, the MTD for FF-10502-01 when administered once weekly for 3 weeks in dogs was determined to be 2.5 mg/kg/dose.

4.5 Dose Rationale

The toxicity of FF-10502-01 was evaluated in two repeat-dose GLP studies conducted in the rat and the dog, as described respectively in Sections 4.4.1.2 and 4.4.2.2 above. Both studies were conducted over a range of doses IV weekly x 3 weeks followed by a 2-week recovery period. Findings typical of a pyrimidine nucleoside analogue were determined, including lympho-hematopoietic organ hypocellularity (bone marrow, thymus and spleen) and decreased spermatogenesis (rat). Changes were generally reversible following the 14-day recovery period. The MTD was found to be 250 mg/kg (1500 mg/m^2) in the rat and 2.5 mg/kg (50 mg/m^2) in the dog. The dog was the more sensitive of the 2 species; therefore, the proposed starting dose in the human was 1/6 of the MTD in the dog, or 8 mg/m^2.

In the Phase 1 study of FF-10502-01, a single dose escalation schema was followed until observation of ≥ Grade 2 toxicity, which was observed in the first dose cohort. At that point, a standard 3+3, dose-escalation schema was followed.

In the dose-escalation phase of the study, a cumulative total of 38 patients (19 male, 19 female) were enrolled on study in 9 dose cohorts over a dose range of 8-135 mg/m^2. Preliminary data suggest that FF-10502-01 is well tolerated and demonstrates early signals of clinical activity. Partial responses have been demonstrated in two patients with cholangiocarcinoma, one at Cohort 5 (40 mg/m^2) through 10 cycles, and one at Cohort 6 (60 mg/m^2) through 4 cycles. Three additional patients with cholangiocarcinoma demonstrated stable disease over 2 to 8 cycles. Two additional partial responses have been demonstrated, one in a patient with chondroblastic osteogenic sarcoma (Cohort 3, 18 mg/m^2) who achieved an unconfirmed partial response (73% decrease) in a maxillary mass, and one in a patient with bladder cancer at Cohort 8 (135 mg/m^2). Stable disease has been demonstrated in an additional six patients, one each with pancreatic, prostate, breast, and adenoid cystic carcinoma of the oropharynx, and two with parotid cancer.

The principal toxicities appear to be gastrointestinal (GI), which can largely be mitigated by standard prophylactic anti-emetic medications. One event of Grade 3 nausea which met DLT definition was observed at 40 mg/m^2 despite pre-medication. Grade 1/2 fever, chills, and rash are also commonly observed. Cytopenias have been infrequent, with Grade 1/2 treatment-related anemia reported in only 5 patients, one Grade 3 event of neutropenia at

135 mg/m^2, and no clinically significant thrombocytopenia. Five patients were dose reduced for AEs of mild dysgeusia, severe hypotension, life-threatening hypotension and moderate to severe fatigue, all possibly-related to study drug. Dose escalation was terminated at 135 mg/m^2 due to DLT of infusion-like reactions (pyrexia, chills, Grade 3/4 hypotension). Grade 3 fatigue and ≥ Grade 1 rash were observed at an intermediate dose level of 100 mg/m^2 subsequently evaluated, and the RP2D for the Phase 2a expansion is 90 mg/m^2.

As PD-1/PD-L1 inhibitors are now being used for the treatment of urothelial cancers, in Cohort 13, the dose of 90 mg/m^2 will be used but in a schedule that matches that of PD-1/PD-L1 inhibitor therapy. Namely, FF-10502-01 will be administered IV on Days 1 and 8 of a 21-day cycle.

In the Phase 2a expansion, 36 patients were enrolled at the time of writing this protocol amendment. One patient in the expansion phase developed progressive multifocal leukoencephalopathy (PML) during the course of the study. The patient received 7 cycles of FF10502-01 for cholangiocarcinoma and presented with classic signs of PML. As is common in human immunodeficiency virus (HIV)-negative PML patients, there were no remarkable changes in the patient's lymphocyte count or in other laboratory parameters. Prior treatments included rituximab, approximately 2 years prior to the onset of PML. While prior rituximab exposure and chemotherapy may have triggered the development of PML, the contribution of FF10502-01 to the development of PML cannot be excluded.

5 STUDY OBJECTIVES

5.1 Primary Objective:

- To determine the safety profile, maximum tolerated dose (MTD), dose-limiting toxicities (DLT) and recommended Phase 2 dose (RP2D) in patients who receive FF-10502-01 for advanced solid tumors

5.2 Secondary Objectives:

- To determine the overall response rates
- To determine the duration of response and duration of stable disease (SD)
- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)
- To evaluate the PK of FF-10502
- To evaluate FF-10502 incorporation into whole blood cellular DNA as a pharmacodynamic marker

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a Phase 1/2a, dose-escalation study of FF-10502-01. A total of up to N=161 patients with advanced solid tumors, including lymphomas (for Phase 1 only), will be included.

Major selection criteria are: age ≥ 18 years, histologically confirmed solid tumor or lymphoma (lymphoma in Phase 1 only), with documented disease progression following previous therapy. Patients must be ≥ 4 weeks beyond chemotherapy (or ≥ 5 half-lives for targeted agents, whichever is shorter), radiotherapy, major surgery, or other experimental treatments, and recovered from all acute toxicities (≤ Grade 1), have adequate renal and hepatic function, and no known history of significant cardiac disease.

Phase 1:

Following Screening, a total of up to 9 cohorts each will receive FF-10502-01 intravenously (IV) in 500 mL normal saline over a 1-hour period at doses of 8, 12, 18, 27, 40, 60, 90, 135 or 200 mg/m^2 weekly (Day 1, 8, 15) for three weeks, repeated every 28 days (= 1 cycle) until progression of disease.

Dose-limiting toxicity will be defined as the following drug-related events: Grade 4 thrombocytopenia of any duration; other Grade 4 hematologic toxicity lasting ≥ 7 days; ≥ Grade 3 non-hematologic toxicity (excluding Grade 3 nausea, vomiting or diarrhea that is adequately controlled with supportive care and resolves to ≤ Grade 2 within 48 hours); failure of Grade 3 platelets, absolute neutrophil count (ANC), or hemoglobin (Hb) to recover to Grade ≤ 1 within 4 weeks despite use of platelet and red blood cell (RBC) transfusions and/or growth factors; febrile neutropenia (defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour); Grade 3 or 4 thrombocytopenia of any duration associated with bleeding; or other toxicity-related treatment interruption that does not resolve to ≤ Grade 1 by Day 28 when the toxicity has received appropriate medical treatment.

A single-patient dose escalation schema will be followed until the observation of ≥ Grade 2 toxicity. One patient per cohort will be dosed and followed for 28 days through Cycle 1 for DLT. If no ≥ Grade 2 toxicity is seen, the next patient will be enrolled at the next dose level. Dose escalation will proceed in this manner until Grade 2 or greater toxicity is observed in at least one patient per cohort during the first 28 days. At that point, the current dose cohort will be expanded to 3 patients before proceeding in standard 3+3 manner. The dose escalation in subsequent cohorts will proceed in standard 3+3 manner. For all patient cohorts, if 1 of 3 patients per cohort experiences DLT, the cohort will be expanded to 6. If 2 or more of 6 patients per cohort experience DLT, all further dose escalation will stop. If the next lowest dose has only 3 patients, 3 more patients will be treated at that dose to verify it as the MTD. If that dose turns out to be too toxic, then this process will be repeated until the MTD is found through dose de-escalation. All patients will be followed for 28 days for DLT. If 0 of 3 or ≤ 1 of 6 patients per cohort experience DLT by Day 28 following dosing of FF-10502-01, dose escalation will proceed to the next cohort. The highest dose level below the dose level eliciting DLT in ≥ 2 patients will be declared the MTD. A total of 6 patients will be treated at the MTD. The MTD will be declared the RP2D. No intra-patient dose escalation will be allowed from previous dose levels until at least one patient has completed Cycle 1 at the higher dose level, with no Grade 2 or greater toxicities observed.

Dose level adjustments for DLT will be made. Patients who experience DLT at the first dose level, 8 mg/m^2, will not be dose-reduced, and will be discontinued.

During the study, a Safety Review Committee (SRC) consisting of the actively recruiting investigators, the Medical Monitor, and FPHU, will review data from each cohort on an ongoing basis. Intermediate dose levels may be added if DLT is observed and it is recommended to do so by the SRC. Up to 54 patients are planned for Phase 1.

Phase 2a:

Once 6 patients are treated at the MTD in Phase 1, an additional 4 cohorts will be enrolled. Cohort 10 will enroll any patient with an advanced solid tumor who is otherwise eligible for this study (up to 20 patients). Cohort 11 will enroll patients with cholangiocarcinoma (up to 50 patients). Cohort 12 will enroll patients with carcinoma of the gallbladder (up to 10 patients). Cohort 13 will enroll patients with urothelial carcinoma (up to 27 patients).

Eligible patients enrolled in Phase 1 at the MTD may count towards the Phase 2a accrual.

Cohorts 1 to 12 (Both Phases):

Patients in Cohorts 1 to 12 will receive FF-10502-01 on a weekly schedule for 3 weeks (Days 1, 8, and 15), repeated every 28 days. The Phase 2a dose regimen is FF-10502-01 90 mg/m^2, administered on Days 1, 8, and 15 of a 28-day cycle.

Blood samples for PK assessment of FF-10502 plasma concentrations for patients in Cohorts 1 to 12 will be collected on Cycle 1 Days 1 and 15 pre-dose, immediately following cessation of infusion (within 15 minutes), between 1-2 hours post-infusion, and between 4-6 hours post-infusion. Incorporation of FF-10502 into cellular DNA of whole blood will be assessed as a pharmacodynamic endpoint pre-dose Cycle 1, Days 1, 8, and 15, and during the Day 22 visit.

Blood for hematology and serum chemistry determinations will be collected within 28 days before Cycle 1 Day 1, on Days 1, 8, 15 and 22 of Cycle 1, on Day 1 of each subsequent cycle and at the End of Treatment Visit. After Cycle 1, blood for hematology also will be collected pre-dose on Days 8 and 15 of each cycle. Urine will be collected for urinalysis within 28 days before Cycle 1 Day 1, on Day 1 of each cycle and at the End of Treatment Visit.

Cohort 13 (Phase 2a):

Patients in Cohort 13 (urothelial carcinoma) will receive FF-10502-01 on a weekly schedule for 2 weeks (Days 1 and 8), repeated every 21 days.

Blood samples for PK assessment of FF-10502 plasma concentrations for patients in Cohort 13 will be collected on Cycle 1 Days 1 and 8, pre-dose, immediately following cessation of infusion (within 15 minutes), between 1-2 hours post-infusion, and between 4-6 hours post-infusion. Incorporation of FF-10502 into the cellular DNA of whole blood will be assessed as a pharmacodynamic endpoint pre-dose on Cycle 1 Days 1 and 8; and at any time during the Cycle 1 Day 15 visit. Blood for hematology and serum chemistry determinations will be collected within 28 days before Cycle 1 Day 1, on Days 1, 8, and 15 of Cycle 1, on Day 1 of each subsequent cycle, and at End of Treatment. After Cycle 1, blood for hematology also will be collected pre-dose on Day 8 of each cycle. Urine will be collected for urinalysis within 28 days before Cycle 1 Day 1, on Day 1 of each cycle, and at the End-of-Treatment Visit.

All Cohorts (Both Phases):

Disease assessments, based on computed tomography (CT) and/or magnetic resonance image (MRI), will be obtained at Week 8 and every 8 weeks thereafter until documented progression of disease (PD) for Cohorts 1 to 12; and at Week 6 and every 6 weeks thereafter until documented PD for Cohort 13. Patients who demonstrate clinical benefit will be allowed to continue therapy with FF-10502-01 until progression of disease, observation of unacceptable adverse events, intercurrent illness or changes in the patient's condition that prevents further study participation.

Safety will be assessed through the monitoring of AEs, clinical laboratory parameters (hematology, serum chemistry), vital sign measurements, and physical examinations. Adverse events will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Efficacy assessments for solid tumors will be made according to the Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1)[1].

Mean plasma concentrations of FF-10502 will be determined at each time point for evaluation of dose-linearity. Because a limited number of plasma concentrations will be determined, full determination of routine PK parameters may not be possible. In addition to mean plasma concentrations, as the data allow, additional PK analyses will be provided (trough levels, $t_{1/2}$, T_{max}, C_{max}, AUC, etc). In Phase 2a, population PK methods will be utilized to characterize the PK profile of FF-10502.

FF-10502 incorporation into the cellular DNA of whole blood will be determined as a pharmacodynamic endpoint. In Phase 2a expansion, PK data along with the pharmacodynamic data will be correlated with clinical outcome.

The SRC will review patient data at least quarterly and make recommendations to FPHU regarding the conduct of the trial. Details of the SRC will be outlined in a separate SRC Charter. Study stopping criteria are defined in Section 8.4.3.

6.2 Number of Patients and Centers

Phase 1: Up to 54 patients are planned for the dose-escalation phase, with 6 of these patients treated at the MTD.

Phase 2a: Four additional cohorts are planned; Cohort 10 (advanced solid tumors) will enroll up to 20 patients, Cohort 11 (cholangiocarcinoma) will enroll up to 50 patients, Cohort 12 (gallbladder carcinoma) will enroll up to 10 patients, and Cohort 13 (urothelial carcinoma) will enroll up to 27 patients for a total of up to 107 patients.

Entire study: Total N of up to 161 patients.

The study will be conducted at The University of Texas M.D. Anderson Cancer Center, Filip Janku, M.D., Principal Investigator (PI) and Sarah Cannon Research Institute, Denver, CO, Gerald Falchook, M.D., PI. Drs. Janku and Falchook will serve as Co-PIs for the study. Once experience is gained at these institutions. Up to six additional sites may be added to complete study enrollment in a timely manner.

6.3 Duration of Study

Accrual for the Phase 1 dose escalation phase was approximately 24 months. Accrual for the Phase 2a expansion phase is expected to be up to 21 months, with the last patient followed up to 6 months. The total study duration is expected to be approximately 57 months, through the last patient's last follow-up. The anticipated Phase 2a accrual rate is 3 – 5 patients per month for Cohort 10 and 1-2 patients per month for patients with cholangiocarcinoma, gallbladder cancer, or urothelial carcinoma (Cohorts 11, 12, and 13).

6.4 Criteria for Termination of the Study

If the sponsor, investigator, study monitor, or officials from the Food and Drug Administration (FDA) discover conditions arising during the study that indicate that the study should be halted

or that the study site should be terminated, this action may be taken after appropriate consultation between the sponsor and investigator.

Conditions that may warrant termination include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of an investigator to enroll patients into the study at an acceptable rate
- Failure of an investigator to comply with pertinent FDA regulations
- Submission of knowingly false information from the study site to the sponsor, study monitor, or the FDA
- Insufficient adherence to protocol requirements

Study termination and follow-up would be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

7 STUDY POPULATION

7.1 Inclusion Criteria

Patients must meet all of the following criteria to participate in the study:

- Males and females ≥ 18 years of age
- Patients must meet one of the following criteria:
  - **Cohorts 1 to 10**: Histologically or cytologically confirmed advanced or metastatic solid tumor or lymphoma (lymphoma in Phase 1 only), that is refractory to standard therapy, relapsed after standard therapy, or for which no standard therapy available that is expected to improve survival by at least three months (Cohort 10 in Phase 2a)

    Or
  - **Cohort 11 (Phase 2a):** Histologically or cytologically confirmed intra- or extra-hepatic cholangiocarcinoma that is refractory to standard therapy, relapsed after standard therapy, or for which no standard therapy available that is expected to improve survival by at least three months

    Or
  - **Cohort 12 (Phase 2a)**: Histologically or cytologically confirmed metastatic and/or unresectable gallbladder carcinoma that has progressed on gemcitabine-based therapy or another systemic therapy and for whom a clinical trial is an appropriate option

    Or
  - **Cohort 13 (Phase 2a)**: Histologically or cytologically confirmed metastatic and/or unresectable urothelial carcinoma that has progressed despite platinum-based therapy. (Note: evidence of progression within 12 months of peri-operative platinum-based therapy will be considered to have met progression criteria.) Patients must also have received a PD-1 or PD-L1 inhibitor and progressed or be ineligible for PD-1/PD-L1 inhibitor therapy or have refused such therapy.
- At least 4 weeks beyond the last chemotherapy (or ≥ 5 half-lives for targeted agents, whichever is shorter), radiotherapy, major surgery or experimental treatment and recovered from all acute toxicities (≤ Grade 1)
- Adequate performance status: Eastern Cooperative Oncology Group (ECOG) ≤ 2 (See APPENDIX A)
- Life expectancy of ≥ 3 months
- Adequate hematologic parameters without ongoing transfusional support:
  - Hemoglobin (Hb) ≥ 9 g/dL
  - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 cells/L
  - Platelets ≥ 100 x 10^9 cells/L
- Prothrombin time and activated partial thromboplastin time < 1.5 × the ULN for the institution. Exceptions are permitted following approval by the Medical Monitor
- Adequate renal and hepatic function:

  - Creatinine ≤ 1.5 x the upper limit of normal (ULN), or calculated creatinine clearance ≥ 60 mL/minute x 1.73 m^2 per the Cockcroft-Gault formula. Patients enrolled in Cohort 13 (urothelial cancer) must have a calculated creatinine clearance of >30 mL/minute x 1.73 m^2 per the Cockcroft-Gault formula.
  - Total bilirubin ≤ 2 times the ULN unless due to Gilbert's disease
  - ALT and AST ≤ 2.5 times ULN, or < 5 times ULN for patients with liver metastases
- QT interval corrected for rate (QTc) ≤ 480 msec on the electrocardiogram (ECG) obtained at Screening
- Negative serum pregnancy test within 14 days prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months). Sexually active WCBP and male patients must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the completion of study treatment.
- Ability to provide written informed consent

7.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

- Serious cardiac condition within the last 6 months, such as uncontrolled arrhythmia, myocardial infarction, unstable angina or heart disease defined by the New York Heart Association (NYHA) Class III or Class IV (See APPENDIX B)
- Active central nervous system (CNS) malignant disease in patients with a history of CNS malignancy. Patients with stable, previously or currently treated brain metastases are allowed.
- Known positive for HIV, hepatitis B virus surface antigen (HBsAg), or positive hepatitis C antibody. Patients with positive HBsAg, low Hep B DNA, and normal LFTs and patients with low hepatitis C RNA may be considered for enrollment following discussion with the medical monitor.
- Active infection requiring IV antibiotic usage within the last week prior to study treatment
- Any other medical intervention or other condition which, in the opinion of the PI, could compromise adherence to study requirements or confound the interpretation of study results
- Pregnant or breast-feeding

7.3 Discontinuation of Patients

7.3.1 Procedures for Withdrawal

Any patient may be removed from study for the following reasons:

- Patient withdrawal of consent
- Patient noncompliance

- An increasing or unexpected pattern of unacceptable toxicity
- Disease progression
- Investigator judgment when the well-being and best interest of the patient is compromised

Patients experiencing unacceptable toxicity should be removed from the study once complete resolution of toxicity has been documented. Individual patients may be discontinued from the study by the investigator or sponsor at any time if either determines that it is not in the best interest of the patient to continue.

Any patient who becomes pregnant during the study must be discontinued from study treatment immediately but should be followed through delivery or termination of the pregnancy. Patients should also notify the investigator if they become pregnant within 28 days following the last dose of study drug. FPHU/Westat also must be notified if a patient becomes pregnant on study.

If a patient is discontinued from the study before completing the specified duration of treatment, they should be encouraged to complete the end-of-study assessments and to agree to report any serious adverse events for 28 days following the last dose of study drug. The date the patient is withdrawn and the primary reason for discontinuation will be recorded on the case report form (CRF).

7.3.2 Replacement of Study Patients

Patients who are screened, but do not receive FF-10502-01, will be replaced.

8 STUDY TREATMENT

8.1 FF-10502-01 Investigational Product Description

FF-10502-01 is a pyrimidine nucleoside antimetabolite anticancer drug for IV administration. Nucleoside analogues exert cell cycle phase-specific activity by primarily killing cells undergoing DNA synthesis (S-phase), thus blocking the progression of cells through the G1/S-phase boundary.

The FF-10502-01 20 mg/mL drug product is manufactured by University of Iowa Pharmaceuticals (Iowa City, IA, USA) and will be provided to clinical study sites directly from the drug distribution center designated by FPHU.

8.2 Study Drug Administration

Patients should be scheduled to begin study therapy following completion of Screening.

FF-10502-01 is compatible with both dextrose 5% in water (D5W) and 0.9% sodium chloride (normal saline; NS) when diluted to a final concentration between 50 µg/mL and 1.5 mg/mL. After admixture, the final IV admixture may be maintained at room temperature or under refrigeration (2-8°C) for up to 24 hours. The infusion will be administered over a 1-hour period.

Phase 1: Patients will receive FF-10502-01 weekly IV at the dose level prescribed per cohort on Days 1, 8 and 15 of each 28-day cycle (= 1 cycle).

Phase 2a, Cohorts 10 to 12: Patients will receive FF-10502-01 90 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle (= 1 cycle).

Phase 2a, Cohort 13: Patients will receive FF-10502-01 90 mg/m^2 IV on Days 1 and 8 of each 21-day cycle (= 1 cycle).

8.3 Treatment Duration

Treatment will continue until confirmation of disease progression, unacceptable toxicity, or patient decision to discontinue therapy.

8.4 Dosing Delays, Dose Modifications Due to Toxicity, and Study Stopping Criteria

8.4.1 Toxicity Grading Criteria

Toxicity grading is based on NCI Common Terminology Criteria for Adverse Event v 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

8.4.2 Instructions Regarding Dose Delays and Dose Modifications

Adverse events considered for treatment interruption and dose reduction will exclude the events assessed by the investigator as exclusively related to underlying disease or medical condition/concomitant treatment. If treatment must be delayed for reasons other than toxicity, contact the Medical Monitor to discuss the reasons for delay and plans for resuming study therapy.

- Treatment may be delayed up to 14 days. If the patient has completed two cycles and, in the investigator's opinion, is receiving benefit, treatment may be delayed for longer than 14 days and then resumed following a discussion with the Medical Monitor. Patients who require the next treatment cycle to be held for more than 14 days due to ongoing toxicity from the prior cycle should have the dose reduced by 25%.

- Patients who experience a toxicity requiring reduction in dose level may continue treatment at the lower dose level until disease progression or unacceptable toxicity. The dose level may be reduced twice. Patients who continue to require dose modifications beyond this should be discontinued from the trial. Once the dose has been reduced it may not be escalated.
- See APPENDIX C for FF-10502-01 dose modification requirements.

8.4.3 Study Stopping Criteria

The occurrence of any new cases of PML will prompt FPHU to immediately halt any recruitment and consult with the FDA as the details of the new case are acquired. Details include confirmation of diagnosis per established criteria, history of past medication associated with PML and other items of interest. Treatment of other patients on study may be withdrawn upon consultation with the FDA and investigators.

8.5 Supportive Care Guidelines

- Medications may be administered for the management of symptoms associated with the administration of FF-10502-01, as required.
- Adequate treatment for nausea and/or vomiting and diarrhea is permitted at the discretion of the Investigator.
- Infusion reactions were reported at the RP2D of 90 mg/m^2; pre-treatment with corticosteroids or other medications may be given at the Investigator's discretion.
- Granulocyte stimulating growth factors (eg, G-CSF or GM-CSF) are not allowed during Cycle 1 except for the following situations: Grade 4 neutropenia lasting ≥ 7 days, failure of ≥ Grade 3 ANC to recover to Grade 1 within 4 weeks, or febrile neutropenia (defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour). After Cycle 1, use of granulocyte growth factors are allowed for prophylaxis or management of neutropenia.
- Erythropoiesis-stimulating agents, transfusions, etc, are permitted for management of hematologic toxicities.

8.6 Prior and Concomitant Medications and Therapies

8.6.1 Permitted Medications

All medications and other treatments taken by patients 4 weeks before and throughout the study period will be recorded in the CRF module. Any changes in documented, permitted concomitant medications being taken at the beginning of the clinical trial or added during the time the patient is participating in this study must be recorded in the CRF module.

8.6.2 Prohibited Therapy

Concurrent anti-tumor therapy is prohibited other than chronic hormonal therapy (e.g., anastrozole or leuprolide). Any other investigational agent is prohibited.

8.7 Packaging and Labeling

FF-10502-01 will be provided for IV administration in individual doses as a sterile solution as 20 mL in a clear 30-mL capacity glass vial (20 mg/mL, calculated as free base). The study drug

vials will be labeled with product name, strength, Lot No. and other information as per local regulatory requirements.

8.8 Shipping and Storage

FF-10502-01 vials and FF-10502-01 prepared dosing solution should be stored under refrigerated conditions (2 – 8°C).

8.9 Drug Accountability

The investigator must maintain accurate records of receipt of study drug, dispensing information, and the prompt return or destruction of unused supplies. A drug accountability log will be supplied to each clinical site for purposes of recording study drug dispensation for the study and will be monitored by sponsor personnel. If the site has an electronic study drug accountability form that is in keeping with institutional practice and the form collects the same information as the form supplied by the Sponsor, this form may be substituted for the Sponsor's drug accountability form.

Unused or expired FF-10502-01 will be destroyed per institutional policy.

9 STUDY PROCEDURES

See Schedule of Study Procedures in APPENDIX D. Unless otherwise specified, the study procedures listed in the following subsections apply to all cohorts.

9.1 Screening Procedures

The following evaluation includes standard tests that are to be performed within 28 days prior to the first administration of study treatment to determine patient eligibility.

- Administration of informed consent
- Medical history, physical examination and vital signs
    - In addition to the medical history collected at Screening to determine eligibility, patients will be queried to determine whether they have a history of autoimmune disease or treatment associated with an elevated risk of PML. Specifically, patients will be queried about a history of:
        - Systemic lupus erythematosus
        - Rheumatoid arthritis
        - Sjogren's syndrome
        - Dermatomyositis or polymyositis
        - Idiopathic thrombocytopenic purpura
        - Vasculitis (cryoglobulenic, Giant cell etc)
        - Multiple sclerosis and treatment with an integrin inhibitor such as natalizumab
        - Hematologic malignancy such as lymphoma and treatment with rituximab or anti-CD20 therapy

      Medical history pertaining to any autoimmune disease or treatment associated with an elevated risk of PML will be entered in the clinical database but does not constitute eligibility criteria.
- ECOG Performance Status
- Height and weight
- The following lab tests: (See Table 3 for a list of lab tests)
    - Hematology
    - Coagulation parameters
    - Serum chemistry
    - Urinalysis
- β-HCG for WCBP within 14 days prior to the first dose of FF-10502-01
- 12-lead ECG
- Patients may consent to an optional tumor biopsy during screening. (Refer to Section 10.1.13)
- Review of concomitant medications
- Disease-specific assessment (CT, MRI scans)

9.2 Treatment Cycles

9.2.1 Requirements During Treatment Cycle 1

9.2.1.1 Cycle 1, Day 1

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests: (See Table 3 for a list of lab tests)
  - Hematology, if not performed within the previous 72 hours. Note: In addition to total lymphocyte counts, T cell (CD4 and CD8) and B cell counts will be obtained.
  - Serum chemistry, if not performed within the previous 72 hours
  - Urinalysis, if not performed within the previous 72 hours
- Patients who have not done so at screening may consent to an optional tumor biopsy during Cycle 1. (Refer to Section 10.1.13)
- Review of concomitant medications
- Assessment of AEs
- Administration of FF-10502-01 over a 1-hour period
- Peripheral blood collection in EDTA for PK assessments, pre-dose, immediately following cessation of infusion (within 15 minutes), between 1-2 hours post-infusion, and between 4-6 hours post-infusion
- Peripheral blood collection in sodium heparin for pharmacodynamic assessment, pre-dose

9.2.1.2 Cycle 1, Day 8 (±1 day)

- Vital signs
- The following lab tests: (See Table 3 for a list of lab tests)
  - Hematology
  - Serum chemistry
- Patients who have not done so at screening may consent to an optional tumor biopsy during Cycle 1. (Refer to Section 10.1.13)
- Review of concomitant medications
- Assessment of AEs
- Administration of FF-10502-01 over a 1-hour period
- **Cohort 13 only**: Peripheral blood collection in EDTA for PK assessments, pre-dose, immediately following cessation of infusion (within 15 minutes), between 1-2 hours post-infusion, and between 4-6 hours post-infusion

- Peripheral blood collection in sodium heparin for pharmacodynamic assessment, pre-dose

9.2.1.3 Cycle 1, Day 15 (±1 day)

- Vital signs
- The following lab tests: (See Table 3 for a list of lab tests)
  - Hematology
  - Serum chemistry
- Patients who have not done so at screening may consent to an optional tumor biopsy during Cycle 1. (Refer to Section 10.1.13)
- Review of concomitant medications
- Assessment of AEs
- **Cohorts 1 to 12 only**: Administration of FF-10502-01 over a 1-hour period
- **Cohorts 1 to 12 only**: Peripheral blood collection in EDTA for PK assessments, pre-dose, immediately following cessation of infusion (within 15 minutes), between 1-2 hours post-infusion, and between 4-6 hours post-infusion
- Peripheral blood collection in sodium heparin for pharmacodynamic assessment, pre-dose (Cohorts 1 to 12) or any time during visit (Cohort 13)

9.2.1.4 Cycle 1, Day 22 (±1 day) [Cohorts 1 to 12 only]

- Vital signs
- The following lab tests: (See Table 3 for a list of lab tests)
  - Hematology
  - Serum chemistry
- Patients who have not done so at screening may consent to an optional tumor biopsy during Cycle 1. (Refer to Section 10.1.13)
- Review of concomitant medications
- Assessment of AEs
- Peripheral blood collection in sodium heparin for pharmacodynamic assessment during visit

9.2.2 Requirements During Treatment Cycles After Cycle 1 (Cycles 2, 3, 4, etc)

9.2.2.1 Day 1 of Each Cycle (± 2 days)

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests (within 3 days of each cycle – see Table 3 for a list of lab tests):

- Hematology. Note: In addition to total lymphocyte counts, T cell (CD4 and CD8) and B cell counts will be obtained.
- Serum chemistry
- Urinalysis

- Review of concomitant medications
- Assessment of AEs
- Administration of FF-10502-01 over a 1-hour period

9.2.2.2 Day 8 of Each Cycle (±2 days)

- The following lab tests (see Table 3 for a list of lab tests):
  - Hematology
- Review of concomitant medications
- Assessment of AEs
- Administration of FF-10502-01 over a 1-hour period

*9.2.2.3 Day 15 of Each Cycle (±2 days) [**Cohorts 1 to 12 only**]*

- The following lab tests (see Table 3 for a list of lab tests):
  - Hematology
- Review of concomitant medications
- Assessment of AEs
- Administration of FF-10502-01 over a 1-hour period

9.2.2.4 End of Cycle 2 and Every 2 Cycles Thereafter (±3 days)

- Disease-specific assessment (CT, MRI scans)
- Review of concomitant medications
- Assessment of AEs

9.3 At Relapse or Progression of Disease

- Disease-specific assessment (CT, MRI scans)
- Review of concomitant medications
- Assessment of AEs

9.4 End of Treatment (28 days, ± 5 days, from the last dose of Study Drug)

- Physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests: (See Table 3 for a list of lab tests)

  - Hematology. Note: In addition to total lymphocyte counts, T (CD4 and CD8) and B cell counts will be obtained at end of treatment.
  - Serum chemistry
  - Urinalysis
- 12-lead ECG
- Review of concomitant medications
- Assessment of AEs

9.5 Long-term Follow-up

Long-term follow-up will consist of a clinic visit or telephone call every 3 months until death or patient's refusal to participate to assess survival.

10 DESCRIPTION OF ASSESSMENTS

10.1 Safety Assessments

10.1.1 Adverse Event Definition

An adverse event (AE) includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes occurring whether or not temporally associated with study drug administration and whether or not considered related to study drug. This definition includes an exacerbation of pre-existing medical conditions or events, intercurrent illnesses, hypersensitivity reactions, drug interactions, or clinically significant laboratory findings.

An AE does not include the following:

- Medical or surgical procedures, eg, tooth extraction, transfusion, surgery (The medical condition that leads to the procedure is to be recorded as an AE.)
- Pre-existing conditions or procedures present or detected at the start of the study that do not worsen
- Hospitalization for elective surgeries or for other situations in which an untoward medical event has not occurred
- Abnormal laboratory value, unless it is clinically significant
- Overdose of study drug or concomitant medication unaccompanied by signs/symptoms (If sign/symptoms occur, the final diagnosis should be recorded as an AE.)
- Pregnancy by itself, unless a complication occurs during pregnancy leading to hospitalization; in this case (The medical condition that leads to the hospitalization is to be recorded as the AE.)
- A significant worsening of the disease under investigation which is captured as an efficacy parameter in this study and, thus, is not to be recorded as an AE.

10.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that results in any of the following outcomes:

- Death
- Life-threatening, ie, immediate risk of death from the event as it occurred; (This does not include an adverse event that, had it occurred in a more serious form, might have caused death.)
- Persistent or substantial disability/incapacitation
- Results in or prolongs an existing inpatient hospitalization
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.1.3 Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the protocol or elsewhere. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the investigational therapy, but are not specifically mentioned as occurring with the investigational therapy.

10.1.4 Adverse Event Reporting Period

The adverse event reporting period begins from the date of the first dose of study drug to 28 days following the last dose of study drug.

10.1.5 Recording of Adverse Events

Each AE should be recorded in standard medical terminology on the AE CRF module. Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. For example, cough, runny nose, sneezing, sore throat, and head congestion should be reported as 'upper respiratory infection'. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Dates of start (onset) and stop (recovery), action taken, and outcome will be recorded in the AE CRF module.

All clinically significant abnormal changes in laboratory parameters will be recorded as an AE on the AE module, with the following exceptions: clinically significant abnormal laboratory changes determined to be related to the study condition and concomitant conditions, eg, diabetes, of which the investigator was previously aware and that have not worsened.

The investigator will evaluate all AEs with regard to maximum intensity and relationship to study drug, as follows.

10.1.5.1 Maximum Intensity

Maximum intensity should be assigned using one of the severity grades as outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03); if the AE is not specifically listed in CTCAE v4.03, use the following grades:

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening
- Grade 5: death

10.1.5.2 Relationship to Study Drug

The degree of certainty with which an AE is attributed to study drug (or alternative causes, eg, natural history of the underlying diseases, concomitant therapy, etc) will be determined by how well the event can be understood in terms of known pharmacology of the study drug and/or

reactions of similar nature previously observed with study drug. Each AE will be assigned one of the following five categories:

- Not related: There is not a temporal relationship to the study drug (eg, too early, too late), or there is a reasonable causal relationship to another drug, concurrent illness, or circumstance.
- Unlikely related: There is a temporal relationship to study drug, but there is not a reasonable causal relationship between the time of study drug administration and the AE (ie, it is doubtful the AE is related to the study drug); could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
- Possibly related: There is a reasonable temporal sequence from time of study drug administration (eg, occurred in a time frame relevant to study drug dose); or for which the possibility of the study drug being the causative factor (eg, existence of similar reports attributed to the study drug; reactions attributable to the pharmacological effect) could not be excluded, although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
- Probably related: There is a reasonable temporal sequence from time of study drug administration; and for which the possibility of factors other than the study drug administration, such as underlying disease, complications, concomitant drugs, or concurrent treatment, could not be excluded as the cause.
- Definitely related: Follows a clear temporal sequence from time of study drug administration; could not be possibly explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; follows a response pattern known to be associated with study drug administration.

10.1.6 Adverse Event Reporting

Each AE is to be reported by the investigator as serious or non-serious according to the definitions in Section 10.1.2 above. This classification determines the regulatory reporting procedures to be followed as described in Table 2.

Table 2. Reporting Guidelines for Adverse Events

Gravity of AE	Reporting Time to FPHU/Westat	Type of Report
Serious	Within 24 hours after the site becomes aware of the event	Initial SAE Report
Non-Serious	Per AE CRF module	Completed AE CRF Module

Any SAE, regardless of relationship to investigational therapy that occurs within 28 days following the last dose of study drug must be reported to the Medical Monitor within 24 hours after the site becomes aware of the event. The investigator is encouraged to discuss with the Medical Monitor any adverse experiences for which the issue of reportability is unclear or questioned. The initial report should be followed by submission of a more detailed SAE Report when follow-up information is available.

If the SAE occurs more than 28 days after the last dose of study drug, SAEs should be reported only if considered related to FF-10502-01. In the event of patient death, the reason for death should be recorded as the SAE, with 'death' recorded as the outcome on the SAE CRF module.

The SAE also will be recorded as an AE on the AE CRF module. Note: the SAE Report is different from the AE CRF. In areas of both forms where the same data are reported, the forms will be completed in a consistent manner. For example, the same term should be used for the AE on both forms, with the same start and stop dates, action taken, outcome, etc. A checkbox on the AE CRF module for whether the AE resulted in an SAE, will link the two types of report for a given event.

An SAE Report should be prepared with as much available information concerning the event as possible so that a written report can be filed with the appropriate regulatory authorities. If causality cannot be determined definitively at the time of the SAE occurrence, it is important to notify FPHU/Westat within the timeline stated above, and to attribute the relationship as 'Not Assessable' (only applicable for the initial SAE Report). When new significant information is obtained and the outcome and attribution of the event is known, the investigator will communicate this in a follow-up SAE Report. This relevant information will be provided in a timely manner to allow reporting to regulatory authorities within the required reporting period. Any SAE follow-up information requested by FPHU/Westat should be provided in a timely manner.

As necessary, the SAE Report should be accompanied by relevant pages from the CRFs, eg, medical history, AEs, concomitant medications. Additional information may be requested by FPHU/Westat in an expedited manner to ensure that the initial reporting of the SAE made to the regulatory authorities complies with the required time frame. FPHU/Westat may be required to collect and report additional information to the regulatory authorities in a follow-up report, containing a final evaluation of the event, including copies of hospital reports, autopsy reports, or other relevant information.

10.1.7 Adverse Event and Serious Adverse Event Follow-Up

All AEs and SAEs should be followed until resolution, return to baseline, or until the point it is deemed that further recovery is unlikely. All measures required for AE management and the ultimate outcome of the AE will be recorded in the source document and AE CRF module.

10.1.8 Ongoing Safety Evaluation

A study safety evaluation will be conducted on a regular (monthly) basis by teleconference. Dose exposure, dose-limiting toxicity, AE/SAE profiles and clinical laboratory abnormalities, and other safety measures will be reviewed during each convened meeting. Patient accrual will not be interrupted during the regular scheduled safety evaluations. These discussions will be led by the FPHU Medical Monitor and Principal Investigator.

10.1.9 Clinical Laboratory Tests

Clinical laboratory tests include hematology, coagulation parameters, serum chemistry and urinalysis (Table 3). Serum pregnancy testing will be performed at Screening for all women of childbearing potential.

Table 3. Clinical Laboratory Parameters

Hematology	Coagulation Parameters	Serum Chemistry	Urinalysis	Bone Marrow Aspirate/Biopsy (Phase 1; Lymphoma Patients only)
Red blood cell count Hemoglobin Hematocrit White blood cell count Differential: Neutrophils ANC Lymphocytes (total counts for all time points; T cell [CD4 and CD8] and B cell counts on Day 1 of each cycle and at EOT) Monocytes Eosinophils Basophils Platelets	Fibrinogen aPTT PT (INR)	Serum creatinine BUN Glucose (non-fasting) Albumin AST ALT LDH Total bilirubin Total protein Alkaline phosphatase Calcium Phosphorus Magnesium Sodium Potassium Chloride Bicarbonate	pH Blood Nitrates Glucose Ketones Leukocytes Protein Microscopic examination	Percent cellularity Lymphocyte subtype Evaluation (eg, positive, negative, indeterminate) Immunohistochemistry Cytometry

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; EOT, end-of-treatment; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time.

10.1.10 Vital Sign Measurements

Vital sign measurements include temperature, blood pressure and pulse rate. Additional measurements may be obtained if clinically indicated. Any value considered clinically significant by the investigator will be recorded as an AE on the CRF. Clinically significant changes compared to baseline values should be followed until clinical resolution.

10.1.11 Physical Examinations

Complete physical examinations include the following body system evaluations: General Appearance, Skin, Musculoskeletal, Eyes, Ears, Nose, Throat, Cardiovascular, Chest, Abdomen, Lymph Nodes, and Neurological.

Symptom-oriented evaluations will be performed when clinically indicated. Weight will be measured at Screening, Day 1 of each treatment cycle and the End of Treatment Visit.

10.1.12 Electrocardiograms

12-Lead ECGs will be performed at Screening and at End of Treatment.

10.1.13 Tumor Biopsy

A tumor biopsy should be obtained at screening or during Cycle 1 in patients with accessible tissue, if determined to be feasible, in the opinion of the investigator. The biopsy will be used for genetic studies for mutations and other variables to determine tumor molecular subtype which can be important for patients who are candidates for personalized therapy. In addition, laboratory studies using the tumor tissue may be performed.

If the patient's tumor's mutation status has already been characterized these data may be recorded in the clinical database for further analysis.

10.2 Efficacy Assessments

10.2.1 Criteria for Evaluation of Response and Progression

Evaluation of response to treatment and determination of disease progression in patients with solid tumors will be made according to the Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1).[1]

10.2.2 Disease Response Criteria

10.2.2.1 Patients with Solid Tumors

- **Evaluation of Target Lesions in Patients with Measurable Disease:**
  - **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):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
  - **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (**Note**: the appearance of one or more new lesions is also considered progression).
  - **Stable Disease (SD):** Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Evaluation of Non-Target Lesions (all other lesions, or in patients with non-measurable disease only)**
  - **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 one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
  - **Progressive Disease (PD)**: Unequivocal progression of existing non-target lesions, or appearance of one or more new lesions. When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- **Time Point Response**

  At each protocol-specified time point, an overall response assessment should be made. Criteria for overall response for target and non-target disease are summarized in Table 4 and Table 5.

  Table 4. Criteria for Overall Response for Target (+/- Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

Table 5. Criteria for Overall Response for Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

- **Evaluation of Best Overall Response**

  The best overall response is the best response recorded across all time points. If CR or PR is recorded, confirmation should be sought 28 days later. When SD is believed to be the best response, no confirmation is required.

10.2.3 Efficacy Endpoints

10.2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with objective response achieved by Week 16 (Cohorts 1 to 12) or Week 12 (Cohort 13) following FF-10502-01 treatment.

- **Patients with Solid Tumors**

  Objective responses for patients with solid tumors include a best response of complete response (CR) or partial response (PR), as defined above.

10.2.3.2 Secondary Efficacy Endpoints

Duration of Response: length of time from the date of first evidence of response (CR or PR) to date of first evidence of PD

Duration of SD: length of time from the date of the first administration of study drug to the date of first evidence of PD

Progression-Free Survival: length of time from the date of first administration of study drug to the first objective evidence of disease progression or death, whichever is earlier

Overall Survival: length of time from the date of first administration of study drug to the date of death from any cause

10.2.4 Timing of Assessments to Determine Response

Disease assessments will be made at the end of Cycle 2 and every two cycles thereafter. Disease assessments may be made at other time points at the discretion of the Investigator.

10.2.5 Pharmacokinetic Endpoints

Because a limited number of plasma concentrations will be determined, full determination of routine PK parameters may not be possible. In addition to mean plasma concentrations, as the data allow, additional PK analyses will be provided (trough levels, $t_{1/2}$, T_{max}, C_{max}, AUC, etc). In Phase 2a expansion, population PK methods will be utilized to characterize the PK profile of FF-10502.

10.2.6 Pharmacodynamic Endpoints

FF-10502 incorporation into whole blood cellular DNA is expected to increase following treatment in a dose dependent manner, based on mechanism of action. Therefore, as a measure of pharmacologic activity and a preliminary measure of efficacy, FF-10502 incorporation into the cellular DNA of whole blood will be assessed and correlated with clinical outcome.[18] In the Phase 2a expansion, PD data will be combined with PK data to assess the impact of drug exposure on FF-10502 incorporation into DNA.

11 STATISTICAL METHODOLOGY

11.1 Determination of Sample Size

Phase 1:

The sample size reflects requirements associated with a single patient dose escalation until ≥ Grade 2 toxicity is observed, thereafter a 3+3 design. A total of 3 to 54 patients are planned (1 to 6 patients in each of 9 dose cohorts).

Phase 2a:

There are 4 cohorts in Phase 2a. The expansion cohorts will assess the efficacy of FF-10502-01 in a cohort of patients with a variety of solid tumors (Cohort 10), in a cohort of patients with cholangiocarcinoma (Cohort 11), in a cohort of patients with gallbladder carcinoma (Cohort 12), and in a cohort of patients with urothelial carcinoma (Cohort 13).

The primary measure of efficacy in these 4 expansion cohorts will be response according to the RECIST 1.1. criteria. A maximum of 20 patients will be accrued in Cohort 10, a maximum of 50 patients will be accrued in Cohort 11, a maximum of 10 patients will be accrued in Cohort 12, and a maximum of 27 patients will be accrued into Cohort 13.

Cohort 10: Cohort 10 will recruit patients with a variety of solid tumors to explore whether responses are seen in additional tumor types. If the overall response rate amongst these patients is 14%, there will be a less than 5% chance of failing to see a response in at least 1 patient.

Cohort 11 (cholangiocarcinoma): Historically, very low response rates have been observed in cholangiocarcinoma. Cohort 11, with a maximum of 50 patients, has 80% power if the true response rate, p_1, is 16%, using a 1-sided type I error of 5% with a null hypothesis, p_0, of 5%. A Simon 2-stage design will be employed so that 50 patients are only recruited if evidence of activity is confirmed at an interim analysis. If after 25 patients have been recruited, there are 1 or fewer responses, enrollment for this cohort may be suspended for futility. If after 50 patients have been recruited, 6 or more responses are observed, the null hypothesis of a 5% response rate will be rejected. An alternative analysis may include all treated cholangiocarcinoma patients—not just those meeting the definition of Cohort 11.

Stable disease for ≥ 4 cycles (approximately 4 months) may also be of clinical benefit in this population. If the proportion of patients in this cohort having stable disease is ≥30% after 25 patients have been enrolled and treated, enrollment into this cohort may continue until 50 patients are treated. Note that recruitment will continue past 25 patients—it will not stop until a decision is made at the interim analysis.

Cohort 12 (gallbladder carcinoma) is exploratory with 10 patients to be recruited. If the response rate amongst these patients is 26%, there will be a less than 5% chance of failing to see a response in at least 1 patient.

Cohort 13 (urothelial carcinoma) will also employ a Simon 2-stage design with 80% power, a 1-sided type I error of 5%, p_1 =20% and p_0=5%. If after 15 patients have been recruited, there are no responses, enrollment for this cohort may be suspended for futility. If after 27 patients have been recruited, 4 or more responses are observed, the null hypothesis of a 5% response rate will be rejected.

In both Cohorts 11 and 13, there will be no pause in recruitment prior to the interim analysis given the previous responses already observed in these indications. Furthermore, prior to any

decision to stop recruitment into a given cohort, the number of patients with prolonged stable disease will also be considered.

11.2 Analysis Populations

The safety analysis set includes all patients who are administered any fraction of a dose of study drug. For a particular measure, the full analysis set (FAS) includes those patients who have a valid baseline and one or more post-treatment assessments for that measure of interest.

The PK population consists of all patients in the FAS who complete a baseline and at least one follow-up PK assessment.

The pharmacodynamic () population consists of all patients in the FAS who complete a baseline and at least one follow-up pharmacodynamic assessment.

11.3 Statistical Analysis Methods

All data will be analyzed using Statistical Analysis System (SAS Version 9.4 or higher for Windows, SAS Institute, Cary, NC). Continuous variables will be summarized using number, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using number and frequencies.

11.3.1 Safety Analyses

11.3.1.1 Adverse Events

All safety endpoints will be summarized using descriptive statistics and will be based on the safety analysis dataset.

All AEs will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA; Version 15.0 or higher). An AE will be considered a treatment emergent adverse event (TEAE) if the onset is after the first dose of study drug to 28 days following the last dose of study drug or if the condition was present at baseline but worsened after the first dose.

All AEs for each patient will be listed, including intensity grading, relationship to study drug, action taken and outcome. Patient listings of deaths, SAEs, and AEs leading to treatment discontinuation will be provided. Patient narratives will be provided for deaths, SAEs and other significant AEs. Summary tables will be prepared to examine TEAE severity and relationship to study treatment.

AE summaries will be produced separately for each dose cohort and overall, and each disease cohort by dose and overall. All summaries will show, dose cohort and overall, the number and percentage of patients experiencing at least 1 TEAE of each preferred term, arranged by system organ class, and the number of occurrences of the event. Separate summaries will be produced by relationship to study drug, by severity, and for those events with an incidence rate of at least 2% in any group or overall.

SAEs will be summarized in a similar manner; overall, by relationship to study drug, and by severity.

In addition to the above, summaries of the number and percentage of patients discontinuing the study due to AEs and, due to death, will be presented.

11.3.1.2 Laboratory Data

Laboratory data will be listed by patient. Values above and below normal ranges will be indicated, and whether clinically significant. All laboratory values will be graded according to the NCI-CTCAE version 4.03 criteria. Laboratory data will be summarized by actual value and change from baseline using number of non-missing observations (n), mean, standard deviation, median, minimum and maximum. In addition, shift tables and the incidence of Grade 3 or 4 laboratory values will be presented.

11.3.1.3 Vital Signs

Vital signs will be listed by patient. Values above and below normal ranges will be indicated as will clinical significance. Vital sign data will be summarized by actual value and change from baseline using number of non-missing observations (n), mean, standard deviation, median, minimum and maximum.

11.3.1.4 Other Safety Data

Data collected for physical examinations, ECGs and related measures will be listed.

11.3.2 Efficacy Analyses

11.3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in each disease cohort (cholangiocarcinoma, gallbladder carcinoma, urothelial carcinoma, or other solid tumor) with objective response (OR) within 4 cycles of study drug. Thus, this is the proportion of patients in Cohorts 1-12 with an OR within 16 weeks of their first dose of study drug and the proportion of patients in Cohort 13 with an OR within 12 weeks of their first dose of study drug. The OR rate is defined as the proportion of patients in the FAS with a confirmed complete or partial response. Ninety percent confidence intervals for the OR rate will be estimated.

11.3.2.2 Secondary Efficacy Endpoints

Duration of response, duration of SD, PFS and OS curves will be estimated by disease cohort using Kaplan-Meier product limit estimates. Median and 90% confidence interval of time-to-event will be estimated. Progression-free survival will be calculated from the date of first dose of study drug to the date of first documented evidence of disease progression or death, whichever is earlier. Overall survival will be calculated from the date of first dose of study drug to the date of death due to any cause. Patients who did not experience progression or death will be censored at the time of last contact.

11.3.3 Pharmacokinetic Endpoint Analysis

Mean plasma concentrations of FF-10502 will be determined at each time point by dose cohort for evaluation of dose-linearity. Because a limited number of plasma concentrations will be determined, full determination of routine PK parameters may not be possible. In addition to mean plasma concentrations, as the data allow, additional PK analyses will be provided (trough levels, $t_{1/2}$, T_{max}, C_{max}, AUC, etc). Population PK methods will be utilized to characterize the PK profile of FF-10502.

11.3.4 Pharmacodynamic Endpoint Analysis

Pyrimidine nucleoside anti-metabolites exert their activity via cell-cycle specific cell killing, through incorporation into cellular DNA of the target cancer cell. Thus, cells undergoing DNA synthesis (S-phase) are killed, and the progression of cells through the G1/S-phase boundary is blocked. Accordingly, FF-10502 incorporation into the cellular DNA of whole blood will be

determined as a pharmacodynamic endpoint in this study. Change from baseline in FF-10502 cellular DNA incorporation levels will be measured in whole blood collected from each patient during the study. pharmacodynamic parameters from the PD population will be summarized using descriptive statistics including the number of patients, mean, standard deviation, minimum, median, maximum, range, and coefficient of variation. Changes from baseline will be correlated with drug exposure and clinical outcome.

11.3.5 Other Summaries

Demographics will be summarized using descriptive statistics. Medical history findings, concomitant medications, and protocol deviations will be listed but not summarized.

12 STUDY MANAGEMENT

12.1 Data Management

The investigator is responsible for completing and maintaining adequate and accurate source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, discharge summaries, CRF worksheets, etc. Data for this study will be submitted electronically. Access to the database will be provided following a brief on-line training session. Each user will receive a unique username and password, which should not be shared. The investigator must sign the investigator's statement for each patient indicating that the data reported are accurate. See APPENDIX H for Ethical Standards to be followed during the study.

12.2 Monitoring

The sponsor and Westat are responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

12.3 Audits and Inspections

The sponsor, Westat, a regulatory authority, or an IRB may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact FPHU/Westat immediately if contacted by a regulatory agency about an inspection at their site.

12.4 Amendments

Any amendments to the protocol will be written and approved by the sponsor. All amendments must be submitted to the IRB for approval prior to implementing the changes. In some instances, an amendment requires changes to the informed consent form, which also must be submitted for IRB approval prior to administration to patients. If any changes to the CRF are required, Westat will issue supplemental or revised CRF pages on behalf of the sponsor.

12.5 Record Keeping

12.5.1 Health Insurance Portability Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR. Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study patients authorize the use and disclosure of protected health

information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the sponsor. See APPENDIX I for Investigator Obligations.

12.5.2 Financial Disclosure

The investigator shall provide to the sponsor sufficient accurate financial information to allow the sponsor and Westat to submit complete and accurate financial certification or disclosure statements to the FDA. The investigator shall promptly update this information if any relevant changes occur in the course of the study or for one year following completion of the study.

12.5.3 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

12.5.4 Retention of Study Documents

Study-related records must be retained for 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. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor.

The investigator must not destroy any study-related records without receiving approval from the sponsor. The investigator must notify the sponsor in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor must be contacted to arrange alternative record storage options.

13 ADMINISTRATIVE STRUCTURE OF THE STUDY

Westat will be responsible for data management, statistical analyses, and clinical study report writing. Clinical monitors under the direction of Westat will be used to monitor the study. Clinical laboratory parameters will be assessed by local laboratories and results recorded in the CRF module.

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15 APPENDICES

APPENDIX A. Eastern Cooperative Group (ECOG) Performance Status Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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, e.g., 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

* From ECOG, Robert Comis, MD, Group Chair

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX B. New York Heart Association (NYCA) Classification for Heart Failure

NYHA Classification - The Stages of Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class 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.

APPENDIX C. FF-10502-01 Dosing Delays and Dose Modifications

Treatment may be delayed up to 14 days. If the patient has completed two cycles and, in the investigator's opinion, is receiving benefit, treatment may be delayed for longer than 14 days and then resumed following a discussion with the Medical Monitor. Patients who require the next treatment cycle to be held for more than 14 days due to ongoing toxicity from the prior cycle should have the dose reduced by 25%.

Patients who experience a toxicity requiring reduction in dose level may continue treatment at the lower dose level until disease progression or unacceptable toxicity. The dose level may be reduced twice in 25% decrements. For example, if the starting dose was 90 mg/m^2, then first dose reduction is 67.5 mg/m^2, and the 2nd dose reduction is 50 mg/m^2. Patients who continue to require dose modifications beyond this should be discontinued from the trial. Once the dose has been reduced it may not be escalated.

If a patient experiences myelosuppression, FF-10502-01 should be held and restarted according to Table 1.

Table 1. Dose Modification for Myelosuppression

Absolute Granulocyte Count (x 10^6/L)		**Platelet Count (x 10^6/L)**	Action
≤ 1000 (Grade 3 or 4)	**Or**	≤ 50,000 (Grade 3 or 4)	Dose is held until recovery to Grade 2 or better
Upon recovery to			
–>1000 (Grade 2, 1 or normal)	**And**	>50,000 (Grade 2, 1 or normal)	Dose may be 75% or 100% of recommended dose at investigator discretion

Table 2. Dose Modifications for Non-Hematologic Toxicity

Non-Hematologic Toxicity	**Modification**
Grade ≥ 3 lasting ≤ 7 days	Withhold dose until ≤ Grade 1, resume next dose at 100%
Grade ≥ 3 lasting > 7 days	Withhold dose until ≤ Grade 1, resume next dose with a 25% reduction

APPENDIX D. Schedule of Study Procedures

Table 6: Schedule of Procedures for Cohorts 1-12

Study Activity	Screening[1]	Treatment Cycle 1				Treatment Cycles After 1				Progression/ Relapse	EOT[2]	Long-term FU[3]
		D1	D8[4]	D15[4]	D22[4]	D1[5]	D8	D15	End of C2[6,7]			
Signed ICD	X											
Medical history	X											
Physical examination	X	X[8]				X[8]					X	
Vital signs	X	X	X	X	X	X					X	
ECOG PS	X	X				X					X	
Height	X											
Weight	X	X				X					X	
Hematology[9]	X	X	X	X	X	X	X	X			X	
CD4, CD8, and B-cell counts		X				X					X	
Coagulation	X											
Serum chemistry[10]	X	X	X	X	X	X					X	
Urinalysis[11]	X	X				X					X	
β-hCG (WCBP)	X											
12-lead ECG	X										X	
Concomitant medications	X	Continuous										
AE assessment		Continuous										
Disease response assessment[12]	X								X	X		
Blood for PK assessment[13]		X		X								
Blood for PD assessment[14]		X	X	X	X							
FF-10502-01 administration[15]		X	X	X		X	X	X				

Study Activity	Screening[1]	Treatment Cycle 1				Treatment Cycles After 1				Progression/ Relapse	EOT[2]	Long-term FU[3]
		D1	D8[4]	D15[4]	D22[4]	D1[5]	D8	D15	End of C2[6,7]			
Survival assessment		X	X	X	X	X	X	X	X	X	X	X
Tumor biopsy	X[16]											

Abbreviations: AE, adverse event; β-hCG, beta human chorionic gonadotropin; C, cycle; CT, computed tomography; D, day; EDTA, ethylenediaminetetraacetic acid; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; FU, follow-up; ICD, informed consent documentation; MRI, magnetic resonance imaging; PD, pharmacodynamics; PK, pharmacokinetics; WBCP, women of childbearing potential.

[1] Screening to be performed within 28 days before Cycle 1, Day 1.

[2] End of Treatment visit should be 28 days from last dose of study drug (± 5 days).

[3] Long-term follow-up consists of clinic visits or telephone calls every 3 months to assess survival status.

[4] Day 8, 15, or 22 ±1 day.

[5] Day 1 (window ±2 days).

[6] Day 28 ±3 days.

[7] And every 2 cycles thereafter.

[8] Abbreviated physical exam.

[9] Hematology collected at Screening, Cycle 1 Day 1 (only if not performed in the previous 72 hours), Days 8, 15 and 22, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle), Day 8 and 15 of each cycle (pre-dose) and End of Treatment. See Table 3 for tests to be conducted at each time point.

[10] Serum chemistry collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 72 hours), Days 8, 15 and 22, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Treatment. See Table 3 for tests to be conducted at each time point.

[11] Urinalysis collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 72 hours), Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Treatment. See Table 3 for tests to be conducted at each time point.

[12] Disease Response Assessment may include CT, MRI, and physical exam.

[13] Peripheral blood collected in EDTA for PK assessment Cycle 1 Day 1, Day 15, pre-dose, immediately following cessation of infusion (within 15 minutes), between 1-2 hours post-infusion, and between 4-6 hours post-infusion.

[14] Peripheral blood collected in sodium heparin for PD assessment pre-dose Cycle 1 Days 1, 8, and 15, and during the Day 22 visit.

[15] Prescribed dose (mg/m^2) Day 1, 8, 15 of each 28-day cycle. Phase 2a dose is FF-10502-01 90 mg/m^2 Day 1, 8, and 15 of each 28-day cycle.

[16] Patients may consent to an optional tumor biopsy during screening or during Cycle 1. (Refer to Section 10.1.13).

Table 7: Schedule of Procedures for Cohorts 13

		Treatment Cycle 1			Treatment Cycles After 1			Progression / Relapse	EOT[2]	Long-term FU[3]
Study Activity	**Screening[1]**	**D1**	**D8[4]**	**D15[5]**	**D1[6]**	**D8**	**End of C2[7,8]**			
Signed ICD	X									
Medical history	X									
Physical examination	X	X[9]			X[9]				X	
Vital signs	X	X	X	X	X				X	
ECOG PS	X	X			X				X	
Height	X									
Weight	X	X			X				X	
Hematology[10]	X	X	X	X	X	X			X	
CD4, CD8, and B-cell counts		X			X				X	
Coagulation	X									
Serum chemistry[11]	X	X	X	X	X				X	
Urinalysis[12]	X	X			X				X	
β-hCG (WCBP)	X									
12-lead ECG	X								X	
Concomitant medications	X	Continuous								
AE assessment		Continuous								
Disease response assessment[13]	X						X	X		
Blood for PK assessment[14]		X	X							
Blood for PD assessment[15]		X	X	X						
FF-10502-01 administration[16]		X	X		X	X				

		Treatment Cycle 1			Treatment Cycles After 1			Progression / Relapse	EOT[2]	Long-term FU[3]
Study Activity	**Screening[1]**	**D1**	**D8[4]**	**D15[5]**	**D1[6]**	**D8**	**End of C2[7,8]**			
Survival assessment		X	X	X	X	X	X	X	X	X
Tumor biopsy	X[17]									

Abbreviations: AE, adverse event; β-hCG, beta human chorionic gonadotropin; C, cycle; CT, computed tomography; D, day; EDTA, ethylenediaminetetraacetic acid; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; FU, follow-up; ICD, informed consent documentation; MRI, magnetic resonance imaging; PD, pharmacodynamics; PK, pharmacokinetics; WBCP, women of childbearing potential

[1] Screening to be performed within 28 days before Cycle 1, Day 1.

[2] End of Treatment visit should be 28 days from last dose of study drug (± 5 days).

[3] Long-term follow-up consists of clinic visits or telephone calls every 3 months to assess survival status.

[4] Day 8 ±1 day.

[5] Day 15 ±1 day.

[6] Day 1 (window ±2 days).

[7] Day 21 ±3 days.

[8] And every 2 cycles thereafter.

[9] Abbreviated physical exam.

[10] Hematology collected at Screening, Cycle 1 Day 1 (only if not performed in the previous 72 hours), Days 8, and 15, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle), Day 8 and 15 of each cycle (pre-dose) and End of Treatment. See Table 3 for tests to be conducted at each time point.

[11] Serum chemistry collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 72 hours), Days 8, and 15, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Treatment. See Table 3 for tests to be conducted at each time point.

[12] Urinalysis collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 72 hours), Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Treatment. See Table 3 for tests to be conducted at each time point.

[13] Disease Response Assessment may include CT, MRI, and physical exam.

[14] Peripheral blood collected in EDTA for PK assessment Cycle 1 Day 1, Day 8, pre-dose, immediately following cessation of infusion (within 15 minutes), between 1-2 hours post-infusion, and between 4-6 hours post-infusion.

[15] Peripheral blood collected in sodium heparin for PD assessment pre-dose Cycle 1 Days 1, 8, and during the Day 15 visit.

[16] Prescribed dose (mg/m^2) Day 1 and 8 of each 21-day cycle. Phase 2a dose is FF-10502-01 90 mg/m^2 Day 1 and 8 of each 21-day cycle.

[17] Patients may consent to an optional tumor biopsy during screening or during Cycle 1. (Refer to Section 10.1.13).

APPENDIX E. Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to Good Clinical Practice (GCP), US 21 Code of Federal Regulations (CFR) Part 50, (Protection of Human Subjects), US 21 CFR Part 56 (Institutional Review Boards), International council for Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The U.S. Food and Drug Administration (FDA) regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP and FDA regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records; electronic signatures
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- FDA Guidance for Industry: Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring, August 2013
- FDA Guidance for IRBs, Clinical Investigators, and Sponsors, June 2010
- FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009
- FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE studies, December 2012
- Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, 2018

Copies of these materials are available from the sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- The study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- The potential benefits of the research justify the risks.

FPHU is the sponsor of the Investigational New Drug Application (IND). The sponsor, or designee, if regulatory obligations have been transferred, is responsible for the following:

- Selecting qualified investigators,
- Providing investigators with the information they need to properly conduct an investigation,

- Ensuring proper monitoring of the investigation,
- Ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- Maintaining the IND, and
- Ensuring that FDA and all participating investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.

APPENDIX F. Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the patient informed consent form will be approved by the institutional review board (IRB) before enrollment of any patients. The opinion of the IRB will be dated and given in writing. A copy of the letter of approval from the IRB and a copy of the approved informed consent form will be received by the sponsor prior to shipment of study drug supplies to the investigator.

The investigator will ensure that the IRB will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to patients. The investigator will also ensure that no changes will be made to the protocol without IRB approval.

As a part of the IRB requirement for continuing review of approved research, the investigator will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of patient risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every patient prior to clinical trial participation. The rights, safety, and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines and FDA regulations, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). An FDA Form 1572 will be collected, listing the principal investigator and sub-investigators involved in the study. Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Informed consent must be obtained from every patient before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB-approved consent form and signed by the patient or the patient's legally authorized representative. The Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking patients must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the patient signing it. Another copy must be kept in the investigator's files and made available to and FDA representatives upon request. If, for any reason, patient risk is increased as the study progresses, a revised, IRB-approved consent form must be signed by the patient. Before the study begins, a sample of the consent form must be provided to the sponsor for review. The FDA may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all patients.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB within 5 working days. In this situation, the investigator may not administer any subsequent product to that patient until informed consent and IRB approval are obtained.

Informed Consent

Written informed consent must be obtained from each patient prior to entry in the study. One copy of the signed informed consent document will be given to the patient, and another will be retained by the investigator. Additionally, the participant must be allowed adequate time to

consider the potential risks and benefits associated with his/her participation in the study. The signed and dated consent must be retained with the study records and a copy provided to each participant.

In situations where the participant is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the sponsor and by the investigator's IRB prior to the initiation of the study. The document must contain the eight basic elements of informed consent and may contain the six additional elements described in 21 CFR Part 50. The attached Declaration of Helsinki-provides further details regarding the specific requirements for informed consent. Every consent form must include the following eight elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA and representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the patient's rights and whom to contact in the event of a research-related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or fetus, if the patient is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the patient's participation may be terminated by the investigator without regard to the patient's consent
- Any additional costs the patient may incur from participation in the research

- The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the investigator's part concerning patient consent.

Institutional Review Board (IRB) Ethic Review Committee (ERC) Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit participants, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of participants in the study. It is the responsibility of the investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, International council for Harmonization (ICH) Good Clinical Practices, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the sponsor prior to initiation of the study. Amendments to the protocol will be patient to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the sponsor.

When the sponsor provides the investigator with a Safety Report, the investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the investigator will submit a final report to the IRB/ERC and to the sponsor, if required. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths

Study Files

The investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

Patient Confidentiality

The anonymity of participating patients must be maintained. Patients will be identified by their initials and an assigned patient number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the patient (eg, the signed informed consent document) must be maintained in strict confidence by the principal investigator, except to the extent necessary to allow auditing by the FDA, the clinical monitor, or sponsor personnel.

Investigational Product Accountability

The investigator or designee is responsible for accountability of the investigational product at the site. The investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each patient, and return to the sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The investigator should ensure that the investigational product is used only in accordance with the protocol.