South Plains Oncology Consortium (SPOC)

Protocol: SPOC-2012-001

Phase 1 Dose-escalating Study of MM-398 (Irinotecan Sucrosofate Liposome Injection) plus Intravenous Cyclophosphamide in Recurrent or Refractory Pediatric Solid Tumors

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THE SOUTH PLAINS ONCOLOGY CONSORTIUM ASSUMES NO RESPONSIBILITY FOR THE USE OF THIS EXPERIMENTAL PROTOCOL OUTSIDE THE PARTICIPATING INSTITUTIONS

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1. STUDY SYNOPSIS

SPONSOR:	South Plains Oncology Consortium
PROTOCOL TITLE	Phase 1 Dose-escalating Study of MM-398 (***Irinotecan Sucrosofate Liposome Injection)*** plus Intravenous Cyclophosphamide in Recurrent or Refractory Pediatric Solid Tumors
TRIAL LOCATIONS	Texas, Ohio, Oklahoma, Wisconsin
PROTOCOL NUMBER:	SPOC 2012-001

STUDY OBJECTIVE(S)	**Primary Objective:**
	To determine the Maximum Tolerated Dose (MTD) and safety of MM-398 in combination with intravenous cyclophosphamide in patients with recurrent or refractory pediatric solid tumors
	
	Secondary Objectives:
	• To determine the pharmacokinetic properties of MM-398 in combination with cyclophosphamide in children or young adults with recurrent or refractory solid tumors
	• To measure (within the confines of a phase I study):
	  • Time-to-event efficacy endpoints:
	  ▪ Progression-free survival (PFS)
	  ▪ Time to treatment failure (TTF)
	  • Objective Response Rate (ORR) in patients with Ewing sarcoma, rhabdomyosarcoma, neuroblastoma and osteosarcoma
	
	Exploratory Objective:
	To explore biomarkers associated with toxicity and activity following treatment with MM-398 plus cyclophosphamide. Blood will be collected to enable analysis of metabolic genotype information (e.g. UGT1A1 genotypes). Collection of tumor samples to enable measurement of SLFN-11 expression is encouraged, as SLFN11 expression may be associated with cytotoxic response to topoisomerase inhibitors [54].

STUDY DESIGN	A dose escalating phase 1 study of intravenous MM-398 (given once per three week cycle) together with intravenous cyclophosphamide (daily x 5 doses) in patients with recurrent or refractory pediatric solid tumors. All patients will participate in up to 28 days of screening, during which they will be assessed for eligibility and screened for the UGT1A1*1 and *28 allele. <u>Intravenous Cyclophosphamide Dosing</u> All patients will receive cyclophosphamide 250 mg/m^2 intravenously (given over 30 minutes) daily for 5 days.

MM-398 Dosing

MM-398 will be administered intravenously over 90 minutes on the 3rd day of the 5 day course of cyclophosphamide. The MM-398 + cyclophosphamide regimen will be administered every 3 weeks, unless precluded by progressive disease (radiologic or clinical deterioration) or unacceptable toxicity.

MM-398 will be dose-escalated as follows:

Dose Level	
1A	30 mg/m^2
1	60 mg/m^2
2	90 mg/m^2
3	120 mg/m^2
4	150 mg/m^2
5	180 mg/m^2
6	210 mg/m^2

Pharmacogenomics

Individuals homozygous for the UGT1A1*1 and/or *28 allele (UGT1A1 7/7 genotype) may have increased risk of toxicity from MM-398. Although this phase I study will not be powered to prove an association between UGT1A1 polymorphisms and toxicity, pharmacogenomic data will be collected on all patients and UGT1A1 may be used to stratify patients once an apparent MTD is established. If all of the dose-limiting toxicities that define the MTD occur in patients with homozygous or heterozygous UGT1A1 polymorphisms, then additional patients will be accrued and UGT1A1 genotype will be used stratify patients. Subsequent dose escalation will only include patients with wild-type UGT1A1. Although this may result in a different MTD for each cohort (one for wild-type UGT1A1 and one for heterozygote + homozygotes), all cohorts will be eligible for any expansion cohorts regardless of pharmacogenomics.

*As no patients in the initial dose-escalation phase were identified with UGT1A1 homozygous polymorphisms, there is the potential for high hematopoietic toxicity in such patients at the dosing used in this study. Therefore, all patients will have UGT1A1 polymorphisms assessed. Patients documented not to be homozygous or heterozygous for the UGT1A1*1 and/or *28 allele (UGT1A1 7/7 genotype) may enter at the maximal dose in this study. Patients with homozygous or heterozygous UGT1A1 genotypes, or with results pending will enter at a reduced dose. Patients with pending results entering at a reduced dose may escalate to maximal dose once UGT1A1 results are available.*

Adverse events (AEs) will be evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4 (CTCAE v4). A dose limiting toxicity (DLT) is defined as a toxicity during the first cycle consisting of one or more of the following events:

- Grade 3 or higher non-hematological toxicity (except grade 3 nausea and vomiting, grade 3 diarrhea lasting less than 4 days)
- Grade 4 neutropenia >7 days (stated elsewhere in study)
- Grade 4 thrombocytopenia (stated elsewhere in study)
- Dose delay of >2 weeks due to drug-related toxicity
- Fever with neutropenia is not a DLT (stated elsewhere in study)

Subjects will be enrolled in cohorts of 3 for each dose level. Dose escalation will proceed between each cohort and no intrapatient dose escalation will be allowed. If none of the first 3 subjects experiences DLT, then dose escalation will proceed to the next cohort. If 1 of 3 subjects develops DLT, the cohort will be expanded to 6 subjects. If no more than 1 subject of the 6 experience DLT, then escalation to the next dose level will proceed. If 2 subjects in any dose level experience DLT, the dose escalation will be stopped and the prior dose level declared the MTD. A minimum of 6 evaluable subjects will be treated at the MTD dose level and no more than one of the 6 subjects may experience DLT at this dose level. The MTD will be considered as the recommended dose for future studies. It is estimated that in each of the two UGT1A1 cohorts up to 18 patients will be accrued in order to appropriately evaluate the dose escalation scheme.

At least 6 and up to 12 subjects with Ewing sarcoma (see inclusion criteria) will be entered at the MTD to more accurately estimate the incidence of systemic toxicities, characterize PK, and estimate the response rate. Should fewer than 6 Ewing sarcoma patients be entered onto the study at the MTD, then accrual of 12 Ewing sarcoma patients at the MTD will proceed, which is justified based on the preclinical and molecular marker of response data (in preclinical studies of Ewing sarcoma) for MM-398. The expansion cohort in Ewings sarcoma will occur unless there is no activity or no potential patient benefit observed in Ewing sarcoma patients during the dose-escalation portion of the trial. Similarly an expansion cohort of 12 patients will also be accrued for other histological types for which objective responses are observed that benefit or have the potential to benefit patients, if drug supplies are available for such additional expansion cohorts.

Thus it is estimated that this study may accrue up to 60 patients.

Tumor responses will be measured and recorded according to institutional guidelines, approximately every 6 to 8 weeks by using the RECIST guidelines (version 1.1). The local radiologist and/or PI assessment will determine disease progression.

<u>Pharmacokinetic (PK) studies</u>

Plasma samples for PK will be collected in Cycle 1, from all patients who are homozygous or heterozygous in this study, at the following time points relative to MM-398 infusion:

	Just prior to infusion, and then the following times after infusion completes: 4 hours, 24 hours, 48 hours, 120 hours and 168 hours (all PK are required except the 168 hour time point which is optional). <u>Exploratory Research</u> To explore biomarkers associated with toxicity and efficacy following treatment with MM-398 plus cyclophosphamide, analysis of patient DNA from patient blood will be collected for metabolic genotype information (e.g. UGT1A1 genotypes). In addition, if archived biopsies are available, exploratory protein and mRNA biomarkers will be measured (in particular, SFLN11 expression, as SLFN11 expression may be associated with the cytotoxic response to topoisomerase inhibitors).
ESTIMATED # OF PATIENTS:	Up to 75 subjects: 25 in the dose escalation phase, and an ----- expansion cohort of up to 12 patients total of each histology (Ewing sarcoma, osteosarcoma, neuroblastoma, and rhabdomyosarcoma) which demonstrated an objective response in the dose escalation phase).
INCLUSION CRITERIA:	In order for inclusion, patients must have/be: • Histologically or cytologically-confirmed Ewing sarcoma with confirmation of diagnosis by molecular assessment of t(11:22), breakapart of the EWSR1 gene by FISH translocation or similar translocation in the tumor; rhabdomyosarcoma, neuroblastoma, or osteosarcoma. • Patients in the expansion cohort must have Ewing sarcoma as defined above. • Documented disease progression after prior therapy in locally advanced or metastatic setting. • Disease Status: Patients must have either measurable or evaluable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria from the NCI for assessment of radiographic response. Age 12 months to <21 years at diagnosis. UGTA1A*1 and *28 allele genotype needs to be determined by the treating institution submitting a blood sample to Mayo Clinic BioPharma Diagnostics as per their shipping guidance. Instructions for the sample collection will be provided to the sites. Results are required to begin therapy at the scheduled dose. Patients with pending UGTA1A1 results may receive therapy at a reduced dose and dose adjusted as appropriate once results are complete. • Adequate bone marrow reserves as evidenced by: o Peripheral absolute neutrophil count (ANC) ≥ 1000/mm3 o Platelet count ≥ 100,000/mm3 (transfusion independent), o If subject has platelet count ≤ 150,000/mm3, they will need to be started on dose level 5 in the expansion cohort o Patients with known bone marrow disease will be eligible for study provided they meet the platelet counts following transfusion • Adequate hepatic function as evidenced by:

- Serum total bilirubin less than or equal to 1.5 x ULN

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

- SGPT (Alanine aminotransferase [ALT]) ≤ 3 x ULN
- Serum albumin > 2 g/dL

- Adequate Renal Function Defined As
  - Creatinine clearance or radioisotope GFR >70ml/min/1.73 m2
  - or a serum creatinine based on age/gender as follows:

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy and at least 21 days after the last treatment with systemic cytotoxic chemotherapy.
- Patients 18 years or older will provide written consent. A parent or legal guardian of a patient <18 years of age will provide informed consent and patients 11 to 18 years of age will provide written assent or as per participating institutional policy.
- Although the potential of MM-398 crossing the blood-brain barrier is unknown, patients with brain metastases who meet all other eligibility criteria will not be excluded.

EXCLUSION CRITERIA:

Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria:

- Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1
- History of any second malignancy in the last 5 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years.
- NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
- Uncontrolled active infection or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome
- Known hypersensitivity to any of the components of MM-398, other liposomal products

	• Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study. • Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results, appropriate to age • Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a reliable method of birth control, during the study and for 3 months following the last dose of study drug.
LENGTH OF STUDY:	It is intended that patients will be treated until disease progression or intolerable toxicity occurs. Following treatment discontinuation, patients will return to the study site for a 30-day follow-up visit. After this visit, patients will continue to be followed for overall survival status via phone or clinic visits every 3 months.
STUDY ASSESSMENTS:	See Schedule of Assessments
STUDY TREATMENT(s)	Cyclophosphamide 250 mg/m2 intravenously (given over 30 minutes) daily for 5 days. MM-398 will be administered intravenously over 90 minutes on the 3rd day of the 5 day course of cyclophosphamide. Patients will remain on the same dose for subsequent cycles of treatment. The cyclophosphamide/MM-398 regimen will be administered every 3 weeks, unless precluded by toxicity, disease progression, or other reason for patient discontinuation. Patients with stable disease or improvement may continue MM-398 until disease progression or intolerable toxicity.
Investigational Product(s)	MM-398 (***irinotecan sucrosofate liposome injection)*** is irinotecan (also known as CPT-11) encapsulated in a liposome drug delivery system. It will be supplied as sterile, single-use vials containing 9.5 mL of MM-398 at a concentration of 4.3 mg/ml. MM-398 must be stored refrigerated (2 to 8°C, 36 to 46°F) with protection from light.
SAMPLE SIZE/STATISTICAL CONSIDERATIONS	A standard 3+3 design dose escalation phase I design to determine MTD will be used. The statistical analysis will be descriptive and the use of any inferential statistics will be exploratory. Safety data will be summarized for the safety population, comprising all enrolled subjects who have been administered any study medication. All available data and tabulation of results will be displayed by dose group. At the establishment of the MTD, expansion cohorts of up to 12 patients total of each histology (Ewing sarcoma, osteosarcoma, neuroblastoma, and

	rhabdomyosarcoma) which demonstrated an objective response in the dose escalation phase) will be enrolled. Estimation of the pharmacokinetic parameters will be performed using Non-Linear Mixed Effects Modeling. Additional exploratory analysis may be performed on the PK samples, to help clarify any safety, efficacy or PK issues related to MM-398 that arise during the course of the study.

2. LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
CBC	Complete blood count
CBR	Clinical benefit response
Cl	Clearance
CNS	Central nervous system
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EP	Evaluable Population
EPR Effect	Enhanced Permeability and Retention Effect
ELISA	Enzyme-linked immunosorbent assay
FDA	Federal Food and Drug Administration
GCP	Good clinical practice
HIV	Human Immunodeficiency Virus
IB	Investigator brochure
ICH	International conference on harmonization
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
ITT	Intent to Treat
kD	Kilo Dalton
kg	Kilogram
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MedDra	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	Milliliter
MTD	Maximum tolerated dose
MUGA	Multiple gated accession scan
NCI	National Cancer Institute
NOAEL	No adverse effect level
NSCLC	Non small cell lung cancer
OS	Overall Survival
PFS	Progression free survival
PGx	Pharmacogenetic
PK	Pharmacokinetic
PP	Per Protocol
PROs	Patient reported outcomes

PTT	Partial thromboplastin time
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
$T_{1/2}$	Half-life
TAM	Tumor associated macrophage
TKI	Tyrosine kinase inhibitors
TR	Translational research
ULN	Upper limit of normal
Vss	Volume of distribution at steady state
WBC	White blood count

3. INTRODUCTION

3.1. Solid tumors to be evaluated

Pediatric patients with localized extracranial pediatric solid tumors generally fare well with conventional multimodal therapy; patients with refractory and relapsed disease have a poor prognosis. New therapeutic regimens that combine chemotherapy with targeted anticancer agents merit study in this patient population. Camptothecin-derived agents such as irinotecan and topotecan have been evaluated in a number of bone and soft tissue sarcomas over the last decade. These agents are attractive because they are commercially available, have demonstrated single agent activity, and in some models are synergistic with alkylating agents. During DNA replication, the enzyme Topoisomerase I relieves torsional strain of DNA. Camptothecins exert their cytotoxic effect by stabilizing the transient covalent complex between DNA and Topoisomerase I and preventing religation of DNA. When the replication fork collides with the stabilized complex, double strand DNA breaks and subsequent cell death occurs [1]. Preclinical data have shown camptothecins have greatest activity when combined with alkylating agents [2], possibly because DNA damage from alkylators requires topoisomerase I for cell repair [3]. Consistent with the S-phase specific mechanism of action, activity is enhanced in preclinical experiments by protracted, low-dose administration [4].

3.1.1. Ewing sarcoma

Ewing Family of Tumors (EFT) include Ewing sarcoma (ES) and peripheral primitive neuroectodermal tumors (PNET), and are aggressive malignancies in children, adolescents and adults [5]. Ewing sarcoma is the second most common primary bone cancer in children [6] and is also among the most common soft tissue malignancies of this age group. Advances in treatment of EFT that have led to survival rates of approximately 70% for localized disease, however, outcomes for patients with metastatic or recurrent EFT remain poor [5-8]. New therapies are needed to improve survival for patients with Ewing sarcoma. Camptothecin derivatives such as topotecan and irinotecan have demonstrated activity against Ewing sarcoma, especially in combination with alkylating agents [1]. Previous studies in patients with metastatic, relapsed or refractory Ewing Sarcoma have demonstrated activity of camptothecin-based therapies including topotecan alone [9-11], irinotecan alone [12-14] or irinotecan in combination with other agents [9, 15-21].

3.1.2 Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma in children. The main histologic variants are the embryonal and the alveolar subtypes, found in 60% and 20% of cases respectively [22]. Approximately 80% of alveolar rhabdomyosarcoma have a characteristic translocation involving fusion of the forkhead transcription factor (FKHR/FOXO1) located on chromosome 13 with either the PAX3 or PAX7 transcription factors located on chromosomes 2 and 1, respectively [23]. At least two-thirds of patients with localized disease at diagnosis are cured, however the cure rate for patients with metastatic disease is dismal and carries a 3 year overall survival of approximately 30% [24, 25].

Xenografts from patients with untreated rhabdomyosarcoma have been shown to be highly responsive to irinotecan including xenografts that were resistant to vincristine, melphalan, and topotecan suggesting that irinotecan has a mechanism of resistance different from other agents, including other camptothecin derivatives[26]. Similar to other models, the antitumor activity of irinotecan in rhabdomyosarcoma is highly schedule dependent, an improved tumor responsiveness

was seen following prolonged exposures [4]. This activity has been validated in two single-agent phase II trials [13, 27]. When irinotecan is used in combination with vincristine, 70% response rates in patients with newly diagnosed metastatic rhabdomyosarcoma have been observed in a phase II window study [28]. This combination was also active in patients with relapsed or progressive rhabdomyosarcoma, although the response rates were lower (31.5%) possibly due to prior therapy [29]. Alkylator therapy is part of all frontline treatments, except for low Group/Stage embryonal histology tumors. The combination of cyclophosphamide and topotecan (a camptothecin derivative) has demonstrated activity, but its addition to standard VAC therapy has not improved outcome [30].

3.1.3. Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in childhood[31]. It is a highly aggressive tumor, often presenting with widespread metastatic disease at diagnosis and as many as 50% of patients demonstrate MYCN amplification and are characterized as high-risk at diagnosis[32]. Although recent advances have been made in the treatment of advanced stage neuroblastoma, event free survival for high risk patients is still less than 70%[32]. Irinotecan has demonstrated dose-responsive [33-35] activity against multiple mouse xenograft models of neuroblastoma, including those with high-risk *MYCN* gene amplification [34-36]. Responses in neuroblastoma patients have been reported in five single agent pediatric Phase I trials in which irinotecan was administered using various schedules of administration [37-41]. In addition, the combination of oral irinotecan and oral temozolomide has been studied in the Phase I setting in heavily pretreated children with neuroblastoma. The regimen was well tolerated and 7/14 assessable patients had either an objective response or disease stabilization for >9 weeks on therapy [42]. Similarly, topotecan in combination with cyclophosphamide has shown substantial activity in patients with recurrent tumors [43] and is now included in frontline therapy in recent and ongoing Children's Oncology Group studies.

3.1.4. Osteosarcoma

Osteosarcoma is the most common bone malignancy in children and adolescents. About 2/3 of patients with localized disease are cured with primary tumor resection and multiagent chemotherapy using high dose methotrexate, doxorubicin and cisplatin. Patients with recurrent tumors and those with metastatic disease at diagnosis have a very poor outcome. Alkylators, particularly ifosfamide, but also cyclophosphamide in some trials, have demonstrated some activity, particularly in combination with the topoisomerase II inhibitor etoposide. The role of camptothecin derivatives is less well established, although responses have been reported using the combination of irinotecan and temozolomide.

3.2. MM-398

MM-398 (irinotecan sucrosofate liposome injection, also known as Onivyde) is irinotecan (also known as CPT-11) encapsulated in a nanoliposomal drug delivery system.

Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycampothecin), a member of the topoisomerase I inhibitor class of drugs, is a semi-synthetic and water soluble analog of the naturally-occurring alkaloid, camptothecin. Topoisomerase I inhibitors work to arrest uncontrolled cell growth by preventing the unwinding of DNA and therefore preventing replication. The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug [44-46]. Irinotecan is a prodrug that is

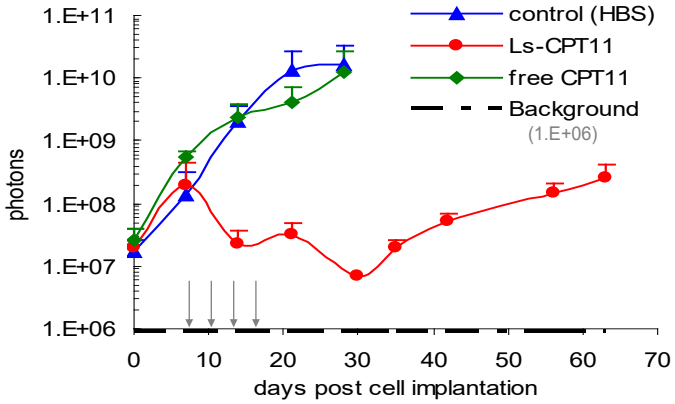
converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38 [45]. SN-38 is cleared via glucuronidation (for which major pharmacogenetic differences have been reported) and biliary excretion. These drug properties contribute to the marked heterogeneities in efficacy and toxicity observed clinically with irinotecan [47]. Hence, drug carrier technologies represent a rational strategy to improve the pharmacokinetics and biodistribution of irinotecan while protecting it from premature metabolism.

MM-398 employs a novel intraliposomal drug stabilization technology for encapsulation of irinotecan into long-circulating liposome-based nanoparticles with high drug load and high *in vivo* stability. The stable nanoliposome formulation of irinotecan has several attributes that may provide an improved therapeutic index. Similar to irinotecan, in which more protracted schedules showed greater preclinical activity[4], the controlled and sustained release should improve activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the more sensitive S-phase of the cell cycle. The long circulating pharmacokinetics, high intravascular drug retention in the liposomes, and enhanced permeability and retention (EPR) effect may potentially result in site-specific drug delivery to solid tumors. Stromal targeting results from the subsequent depot effect, where liposomes accumulating in tumor associated macrophages (TAMs) release the active drug, converting it locally to the substantially more cytotoxic SN-38. The preferentially local bioactivation should result in reduced exposure to potential sites of toxicity and increased exposure to neighboring cancer cells within the tumor. In addition, since SN-38 is not recognized by P-glycoprotein, a drug transporter that plays an important role in acquired drug resistance, MM-398 is likely to be active in tumors resistant to other standard chemotherapies.

3.2.1. Pre-Clinical Experience with MM-398

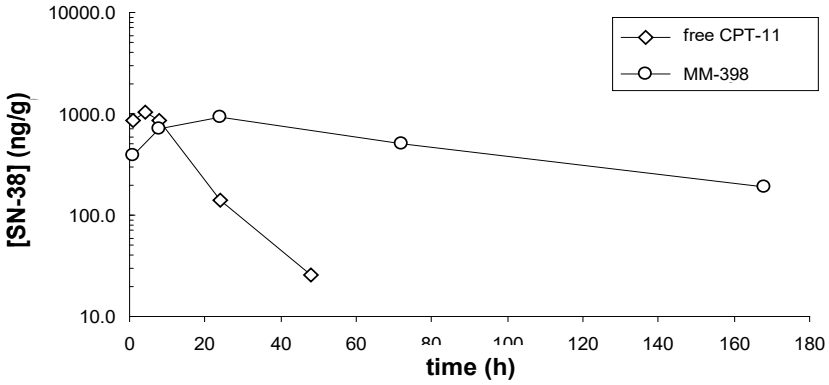
MM-398 has been shown in pre-clinical settings to have a broad spectrum of activity in a wide range of solid tumors including colon, pancreatic, gastric, cervical, non-small cell lung cancer, small cell lung cancer, glioma, thyroid, ovarian, Ewing sarcoma, neuroblastoma, and breast cancers, often with a high degree of anti-tumor activity against resistant or difficult to treat cancer models. Both nanoliposomal irinotecan and immunoliposomal irinotecan showed potent antitumor activity, including durable tumor regressions, and were markedly superior to the equivalent dose of free drug in a bioluminescent-based orthotopic xenograft model of pancreas cancer [48]. In completed and ongoing preclinical studies, promising anti-tumor activity has been observed with MM-398 administration, including multiple complete cures, in both an HT-29 colon carcinoma model [49] and the L3.6pl orthotopic pancreatic cancer model (both of which are well characterized as highly hypoxic preclinical tumor models). The data for the L3.6pl pancreatic tumor is shown in Figure 1. A possible hypothesis that accounts for the observed anti-tumor activity is the effect of macrophages in converting irinotecan to the 1000x more active SN-38 locally, giving rise to a 20-fold increase in the tumor AUC_{SN-38} for MM-398 as compared to free irinotecan (Figure 2). The long duration of exposure allows for prolonged exposure of the slow proliferating cancer cells to the active metabolite as they progress through the cell cycle. In addition, this activity is also hypothesized to result from a reduction in intra-tumoral hypoxia, and the subsequent downstream effects on angiogenesis, metastasis, and the immunosuppressive environment in tumors. Preliminary experiments in the HT-29 model show that MM-398 does reduce markers of hypoxia (Figure 3).

Figure 1: Activity of MM-398 (Ls-CPT11) in an Orthotopic Pancreas Tumor Model Expressing Luciferase (L3.6pl).



Approximately 2.5 x 10^{-5} cells were implanted by direct injection into the pancreas. Bioluminescence images (BLI) were followed over time for tumor burden detection/quantitation. MM-398 and free irinotecan were dosed at a dose of 20 mg/kg/dose weekly for three weeks.

Figure 2: Accumulation of SN-38 in Tumors Following Treatment with Free Irinotecan or Nanoliposomal Irinotecan (MM-398).

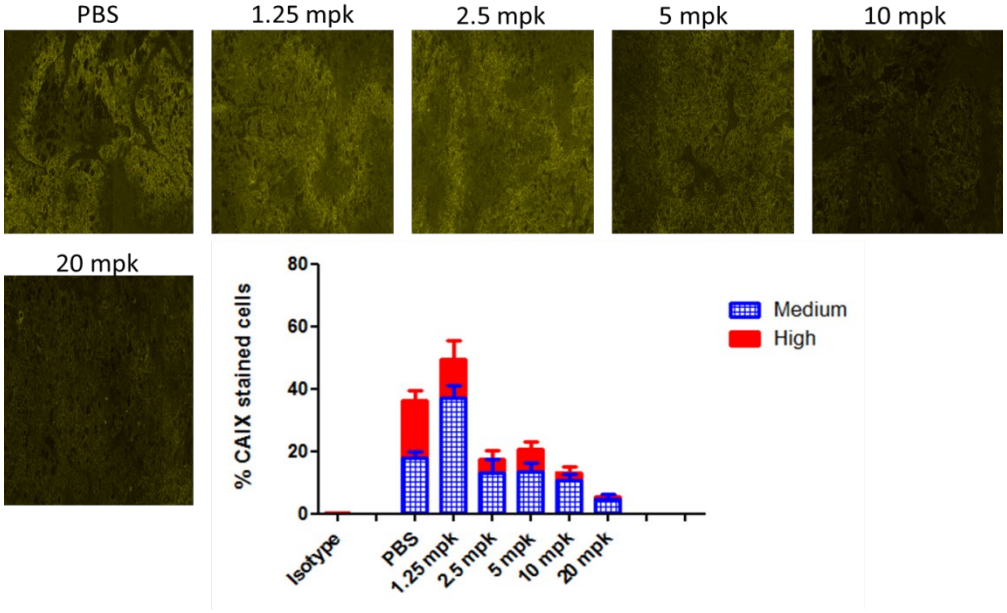


Human colon cancer cells, HT-29, were injected subcutaneously into SCID mice. 40 mg/kg of free irinotecan or MM-398 was injected intravenously when the tumors reached 1000 mm^3 in size. Tumor-bearing mice were sacrificed at different time points, tumors from both groups were extracted and the concentrations of SN-38 were measured

.

In addition to the effect of MM-398 in perturbing the DNA damage repair pathway, liposomal irinotecan formulations have also been ascribed vascular modifying properties [50] We have shown that MM-398 modifies the tumor microenvironment by decreasing the hypoxia marker Carbonic Anhydrase IX staining in hypoxic HT29 xenografts in a dose-dependent manner (**Figure 3**). As hypoxia is a hallmark of resistant and aggressive disease a reduction in hypoxia is expected to make tumor cells more sensitive to chemotherapies [51].

Figure 3: **Effect of MM-398 on Carbonic Anhydrase IX staining in the HT29 xenograft model.**



Human colon cancer cells, HT-29 were injected subcutaneously into nude mice, on day 13 either PBS control or 1.25, 2.5, 5, 10 or 20 mg/kg MM-398 was injected intravenously. MM-398 was dosed once a week for 4 weeks at the indicated doses. Tumors from both groups (n = 5) were extracted 24 hours after the last dose; frozen tumor sections were used for immunohistochemical staining of Carbonic Anhydrase IX (CAIX). Quantification of CAIX staining was performed using Definiens software. Chart shows percentage of CAIX cells stained with medium (middle third) or high (top third) intensity. MM-398 treatment decreases the percentage of both medium and high CAIX positive cells. Representative samples from each group are shown as well as the group average (mean +/- standard deviation)

3.2.2. Clinical Experience with MM-398

MM-398 has been studied in solid tumors, gastric cancer and cervical cancer in adults. Indications currently being studied include pancreatic cancer, colorectal cancer, and glioma. As of February 20, 2013, 292 adult patients have been exposed to MM-398.

Studies that have been completed with MM-398 include, a multi-center, open-label phase 1 dose-escalation study of MM-398 using a once-every-three-week dosing schedule in advanced solid tumor patients (PEP0201); a study of MM-398 in combination with 5-FU/LV in advanced solid tumors (PEP0203); study of MM-398 with or without cisplatin in cervical cancer (PEP0202), which was terminated early; and a randomized phase 2 study of MM-398, irinotecan or docetaxel as a second line therapy in patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (PEP0206).

Studies currently ongoing with MM-398 include, a phase 2 study of MM-398 as a second line therapy for patients with metastatic pancreatic cancer (PEP0208; enrollment is complete and the CSR is being prepared), a randomized phase III study of MM-398 with or without 5-fluorouracil and leucovorin versus 5-fluorouracil and leucovorin in patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy (NAPOLI 1), a pilot study in patients treated with MM-398 to determine tumor drug levels and to evaluate the feasibility of ferumoxytol magnetic

resonance imagining to measure tumor associated macrophages (CITS); and 3 investigator initiated studies which include: a Phase 1 study of MM-398/PEP02 in recurrent high-grade gliomas (UCSF8603); a Phase 1 study conducted by the National Cancer Institute in Taiwan which is to define the MTD and pharmacokinetics of MM-398/PEP02 given as a biweekly regimen in metastatic colorectal cancer (PIST-CRC-01: enrollment completed), and a randomized Phase 2 study of MM-398 in combination with 5-FU/LV and bevacizumab or FOLFIRI + bevacizumab in oxaliplatin pre-treated patients (PEPCOL). **Table 1** and **Table 2** provide a summary of the completed and ongoing studies with MM-398.

Table 1: Summary of Completed Studies with MM-398

	PEP0201	**PEP0202**	**PEP0203**	**PEP0206**
Tumor Type	Advanced solid tumors	Cervical cancer	Advanced solid tumors	Locally advanced or metastatic gastric or GE junction cancer
Phase	1	1	1	2
Current Status	Completed	Terminated	Completed	Completed
No. of patients	11	6	16	44 (MM-398) 44 (Irinotecan) 44 (Docetaxel)
Regimen Schedule	Q3W	Q3W	Q3W	Q3W
Dose level mg/m^2 (n)	60 (1), 120 (6), 180 (4)	60 (3), 80 (3)	60 (3), 80 (6) 100 (5), 120 (2)	120
Combination	n/a	Cisplatin 60 mg/m^2	5-FU/LV; 2000/200 mg/m^2	n/a

Table 2: Summary of Ongoing Studies with MM-398

	UCSF8603	**PIST-CRC-01**	**PEP0208**	**PEPCOL**	**NAPOLI 1**	**CITS**
Tumor Type	Glioma	Colorectal cancer	Metastatic pancreatic cancer	Colorectal cancer	Metastatic pancreatic cancer	Advanced solid tumors
Phase	1	1	2	2	3	1
Current Status	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
No. of patients	28	18	40	47 Total: 24 (MM-398) 23 (Irinotecan)	103 including patients receiving MM-398 or MM-398 + 5-FU/LV	2
Regimen Schedule	Q3W	Q2W	Q3W	Q2W	Q3W (MM-398	Q2W

					Q2W (MM-398 + 5FU/LV)	
Dose level mg/m^2 (n**)**	HT: 60 (3) 90 (5) WT: 120 (6) 180 (4) 240 (3)	80 (6) 90 (6) 100 (6)	120	80	120 (Q3W) 80 (Q2W)	80
Combination	n/a	n/a	n/a	5-FU/LV; 2400/400 mg/m^2 Bevacizumab ; 5mg/kg	5-FU/LV; 2000/200 mg/m^2 (Q2W only)	n/a

HT: patients heterozygous for UGT1A; WT: patients wild type for UGT1A

3.2.2.1. Activity of MM-398

Efficacy results from the other completed studies with MM-398 as a single agent are summarized in the Investigator Brochure (IB).

3.2.2.2. Safety

The clinical safety profile of MM-398 remains similar to that of free irinotecan, of which diarrhea is the most significant adverse event in the treatment, and the incidence of hematological toxicity, predominantly neutropenia, is around 30%. Since the liposome formulation of MM-398 exhibits sustained release profile, longer half-life, higher systemic exposure, slower clearance and smaller volume of distribution of total irinotecan and SN-38 than those of irinotecan which may also alter the safety profile of the drug, further clinical safety data will be collected and investigated in future clinical studies. As of October 2012, no unexpected toxicity has been observed in clinical trials with MM-398.

The overall safety profile of MM-398 is available in the MM-398 Investigator Brochure. In the phase 2 pancreatic cancer study (PEP0208), MM-398 was generally well tolerated, with patients receiving 5 cycles of treatment on average. Infection was the most common SAE. There were three deaths (7.5%) that occurred within 30 days of treatment, which were of an infectious nature and related to neutropenia. A total of 28 patients (70%) experienced at least one treatment-emergent Grade 3 or higher adverse event (CTCAE version 3.0); neutropenia was the most common adverse event (30%) but abdominal pain, asthenia, anemia, hyponatremia, diarrhea, and infection also occurred in > 10% of patients. **Table 3** provides a summary of the adverse events observed in the PEP0208 study (*Note: study is ongoing, but enrollment is complete)*.

Table 3: Summary of Grade 3 or Higher Adverse Events in PEP0208 Study

Adverse Event	N (%)		Adverse Event	N (%)
Neutropenia	12 (30%)		Thrombocytopenia	2 (5%)
Abdominal pain/discomfort	7 (17.5%)		Ulcer	2 (5%)
Fatigue/Asthenia	8 (20%)		Encephalopathy	1 (2.5%)
Anemia	6 (15%)		Febrile Neutropenia	1 (2.5%)
Hyponatremia	7 (17.5%)		Hemorrhage	1 (2.5%)
Diarrhea	6 (15%)		Heartburn	1 (2.5%)
Infection	6 (15%)		AST elevated	1 (2.5%)
Anorexia	4 (10%)		Hypoalbuminemia	1 (2.5%)
Nausea	4 (10%)		BUN elevated	1 (2.5%)
GGT elevated	5 (12.5%)		Hypoglycemia	1 (2.5%)
Hyperglycemia	3 (7.5%)		Confusion	1 (2.5%)
Hyperbilirubinemia	2 (5%)		Pancytopenia	1 (2.5%)
Vomiting	3 (7.5%)		Liver abscess	1 (2.5%)
Alkaline Phosphatase elevated	2 (5%)		Lymphopenia	1 (2.5%)
Ascites	2 (5%)		Pleural effusion	1 (2.5%)
Aspiration Pneumonia	2 (5%)		ALT elevated	1 (2.5%)
Hyperuricemia	2 (5%)		Deep Vein Thrombosis	1 (2.5%)
Hypokalemia	2 (5%)		Obstruction	1 (2.5%)
Pain	2 (5%)		Dyspnea	1 (2.5%)

General Safety of Irinotecan

It has been shown in animal and human pharmacokinetics study that once irinotecan was released from MM-398 liposomes, the conversion of irinotecan to SN-38 is apparently very similar to that of the unencapsulated irinotecan. Because the active pharmaceutical ingredient in MM-398 is the same as irinotecan, the safety profile is anticipated to be similar. In addition to the adverse events noted in Table 3, additional treatment-related adverse effects may be observed. For a full description of the adverse effects of irinotecan please refer to the full prescribing information[52].

3.2.2.3. Clinical Pharmacokinetics

The pharmacokinetic profile of MM-398 single agent was investigated in a phase 1 clinical study (PEP0201) in patients at 60, 120, or 180 mg/m^2 dose levels and in a phase 2 clinical trial in gastric cancer patients (PEP0206) at 120mg/m^2. Plasma levels of total irinotecan, SN-38, and encapsulated irinotecan were measured in these studies.

The peak serum concentrations of total irinotecan (C_{max}) ranged from 48-79 μg/ml for 120mg/m^2 of MM-398, which was approximately 50 fold higher than 125mg/m^2 free irinotecan. The total irinotecan half-life ($t_{1/2}$) for MM-398 ranged from 21 to 48 hours which was approximately 2-3 fold higher than 125mg/m^2 of free irinotecan. Overall total irinotecan exposure at one week (AUC 0–T) ranged from 1200- 3000 μg*h/ml at a dose of 120 mg/m^2 of MM-398, approximately 50-100 fold higher than 300mg/m^2 of free irinotecan. In contrast, SN38 C_{max} levels at 120mg/m^2 of MM-398 ranged from 9 to 17 ng/ml which was approximately 50% less than free irinotecan at 125mg/m^2. Overall exposure of SN38 at one week (AUC 0-T) ranged from 474 to 997 ng*/ml and was only 1-2 fold higher than achieved by free irinotecan at 300mg/m^2. For both SN38 and total irinotecan, the

AUC's increase less than proportionally to the dose of MM-398. The PK parameters of encapsulated irinotecan almost matched that of total irinotecan indicating that most of irinotecan remained encapsulated in the liposomes during circulation. The MM-398 PK parameters are not significantly changed when combined with 5-FU/LV. The tables below summarize the PK findings in previous studies of MM 398.

Table 4: MM-398 PK in q3w (irinotecan, liposome + free drug)

Dose (mg/m^2) & Study / Parameters	PEP0203				PEP0201		PEP0206		Campto® Package insert	
	60 (n = 3)	80 (n = 6)	100 (n = 4)	120 (n = 2)	120 (n = 6)	180 (n = 4)	PEP02 120 (n = 37)	Campto® 300 (n = 27)	125 mg/m^2 (N=64)	340 mg/m^2 (N=6)
C_{max} (µg/mL)	28.93 (± 15.75)	29.16 (± 5.24)	44.06 (± 7.65)	47.94 (± 16.24)	79.4 (± 13.9)	102 (± 17.6)	60.8 (± 36.6)	4.3 (± 1.2)	1.66 (± 0.797)	3.392 (± 0.874)
$t_{1/2}$ (h)	24.02 (± 16.76)	32.09 (± 18.21)	48.11 (± 17.41)	30.65 (± 5.32)	29.5 (± 17.2)	22.2 (± 11.5)	21.2 (± 18.3)	7.7 (± 4.4)	5.8 (± 0.7)	11.7 (± 1.0)
AUC_{0-T} (µg•h/mL)	1,047 (± 1,156)	1,116 (± 810)	2,193 (± 1,017)	1,117 (± 308)	2,835 (± 1,817)	1,945 (± 1,029)	1,651.5 (± 1,412.0)	24.2 (± 7.7)	10.2 (± 3.27)	20.604 (± 6.027)
$AUC_{0-\infty}$ (µg•h/mL)	1,114 (± 1,270)	1,211 (± 924)	2,472 (± 1261)	1,261 (± 500)	2,963 (± 1,947)	1,963 (± 1,035)	1,812.2 (± 1,601.9)	26.2 (± 9.0)	-	-
Cl ($L/h/m^2$)	0.1249 (± 0.1058)	0.1164 (± 0.0 949)	0.0547 (± 0.0358)	0.1033 (± 0.0409)	0.0591 (± 0.0367)	0.119 (± 0.0703)	0.191 (± 0.260)	12.9 (± 4.7)	13.3 (± 6.01)	13.9 (± 4.0)
V_{ss} (L/m^2)	2.6 (± 1.44)	2.93 (± 0.60)	2.63 (± 0.49)	3.16 (± 0.38)	1.8 (± 0.771)	1.97 (± 0.342)	2.23 (± 0.69)	98.5 (± 29.0)	110 (± 48.5)	234 (± 69.6)

Note: AUC 0-T is defined as T = 24 hours for Camptosar package insert [52], T= 49.5 hours for Camptosar in the PEP0206 study and T = 169.5 hours for MM-398.

Table 5: MM-398 PK in q3w (SN-38)

Dose (mg/m^2) & Study / Parameters	PEP0203				PEP0201		PEP0206		Campto® Package insert	
	60 (n = 3)	80 (n = 6)	100 (n = 4)	120 (n = 2)	120 (n = 6)	180 (n = 4)	PEP02 120 (n = 37)	Campto® 300 (n = 27)	125 mg/m^2 (n = 64)	340 mg/m^2 (n = 6)
C_{max} (ng/mL)	7.02 (± 5.64)	7.98 (± 4.39)	7.39 (± 1.68)	16.64 (± 9.36)	9.2 (± 3.5)	14.3 (± 6.16)	8.79 (± 8.68)	44.1 (± 28.2)	26.3 (± 11.9)	56.0 (± 28.2)
$t_{1/2}$ (h)	183.81 (± 172.3)	53.75 (± 15.6)	73.41 (± 18.3)	26.23 (± 6.53)	75.4 (± 43.8)	58.0 (± 32.8)	88.8 (± 114.6)	22.8 (± 10.9)	10.4 (± 3.1)	21.0 (± 4.3)
AUC_{0-T} (ng•h/mL)	367.40 (± 227)	354.77 (± 145)	551.40 (± 381.8)	367.60 (± 155.7)	710 (± 395)	1,160 (± 969)	467 (± 310)	361 (± 125)	229 (± 108)	474 (± 245)
$AUC_{0-\infty}$ (ng•h/mL)	1,373.3 (± 1,119)	502.15 (± 153)	844.28 (± 444)	474.00 (± 209)	997 (± 680)	1,420 (± 1,134)	879 (± 1,426)	440 (± 162)	-	-

Note: AUC 0-T is defined as T = 24 hours for Camptosar package insert [52], T= 49.5 hours for Camptosar in the PEP0206 study and T = 169.5 hours for MM-398.

3.2.2.4. Pharmacogenetics of Irinotecan

The enzyme produced by the UGT1A1 gene is responsible for the glucuronidation of the active metabolite of irinotecan, SN-38. Besides the anti-tumor activity, SN-38 is also responsible for the systemic toxicities associated with irinotecan therapy. Therefore, the glucuronidation of SN-38 to the inactive form SN-38 glucuronide is an important step in reducing the risk of irinotecan toxicity. Patients who carry two deficient alleles of UGT1A1 are associated with reduced glucuronidation of SN-38. Some case reports have described that individuals who are homozygous for UGT1A1*28 alleles and who have fluctuating elevation in serum bilirubin, (the Gilbert's Syndrome patients), may be at greater risk of toxicity upon receiving standard doses of irinotecan. This suggests that there is a link between homozygosity of the UGT1A1*28 allele, bilirubin levels and irinotecan toxicity.

The metabolic transformation of MM-398 (encapsulated irinotecan) to SN-38 in plasma includes two critical steps: (1) the release of irinotecan from liposome and (2) the conversion of free irinotecan to SN-38. Plasma concentrations of encapsulated irinotecan matched approximately with those of total irinotecan, so most of MM-398 was present as the encapsulated form in the plasma. Although the mechanism of release is not understood, it can be expected that once irinotecan leaves the liposomes, it follows the same metabolism of conventional irinotecan. Therefore the genetic polymorphisms in humans predictive for the toxicity and efficacy of MM-398 and those of irinotecan can be considered similar. Nonetheless, due to the smaller tissue distribution, lower clearance, higher systemic exposure and longer elimination half-life of SN-38 of MM398 formulation compared to irinotecan, the genetic polymorphisms may show more association with severe adverse events and/or efficacy for either irinotecan or MM-398.

3.2.2.5. Patients with Reduced UGT1A1 Activity

Based on previous experience with irinotecan, individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan, in a study of 66 patients who received single-agent irinotecan (350 mg/m^2 once every-3-weeks), the incidence of grade 4 neutropenia in adult patients homozygous for the UGT1A1*28 allele was as high as 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype). In other studies a lower prevalence of accompanying grade 4 neutropenia is described. (For details refer to the prescribing information for irinotecan). Importantly the UGT1A1*28 polymorphism has had less of an impact in pediatric patients receiving protracted irinotecan. In 4 clinical trials with over 180 patients, increased toxicity has not been associated with UGT1A1*28 [1, 14, 17, 42, 53]. For this reason, patients who are enrolled on this study and are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) will have treatment initiated at the same dose as patients homozygous or heterozygous for the wild-type allele (UGT1A1 6/6 genotype).

Although this phase I study will not be powered to assess an association of UGT1A1 polymorphisms and toxicity, if an apparent association is observed between UGT1A1 polymorphisms and DLT's is noted, then the UGT1A1 genotype will be used stratify patients for final dose escalation and two separate MTD's will be determined (one for wild type UGT1A1 and one for heterozygote + homozyotes). This will only occur if none of the DLT's that limit further dose escalation beyond an apparent MTD are wild-type for UGT1A1. In the latter case, patients

with wild-type UGT1A1 will continue dose escalation beyond the MM-398 dose level where DLT's prevent further dose escalation of patients with UGT1A1 homozygous or heterozygous polymorphisms.

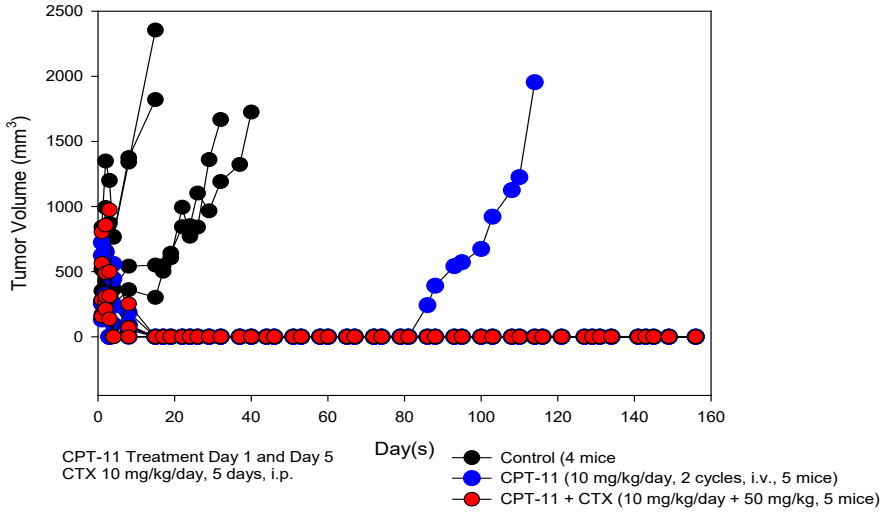
3.2.2.6. Additional genotypic modifiers of irinotecan metabolism

Although the UGT1A1*28 allele is relatively common in Caucasians (estimates 10%), the prevalence is varied in other ethnic groups. Furthermore, additional UGT1A1 genotypes are found with higher prevalence for example in Asian populations and these could be important for the metabolism of irinotecan in these populations. In previous and ongoing studies of MM-398/PEP02 pharmacogenomic information has been collected on patients being enrolled. In the PEP0203 study, the relationship of genetic polymorphism of UGT1A family and DPYD with pharmacokinetic parameters of MM-398 and toxicity did not provide a clear correlation with the small sample size of subjects evaluated in this study. However, the observation that patients with UGT1A1*6/*28 combined polymorphism had higher dose-normalized AUCs of SN-38 and experienced DLT, deserves further exploration.

3.3. Rationale for the Use of MM-398 in combination with cyclophosphamide in Ewing Sarcoma

Testing of MM-398 as a single agent produced complete responses in multiple xenograft models of Ewing sarcoma. Subsequent testing examined a combination of MM-398 given twice a week with daily x 5 days of cyclophosphamide. The preclinical data supporting this study have been published [54]. A representative set of data for that combination is shown in Figure 4, in which testing was carried out on a highly multidrug-resistant, post-myeloablative therapy Ewing xenograft (CHLA-258).

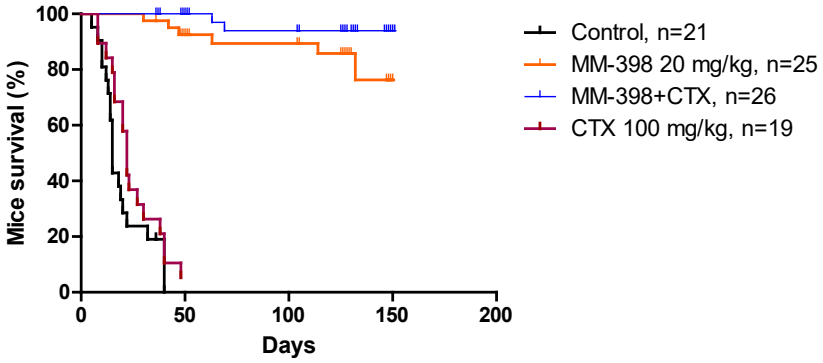
Figure 4: MM-398 with or without cyclophosphamide is active against EFT xenografts



MM-398 was tested alone and in combination with cyclophosphamide (CTX) against 5 EFT xenografts in nu/nu mice, including CHLA-258 and COG-E-352 lines which are highly multidrug-resistant lines established at relapse after myeloablative therapy (Figure 5). MM-398 alone was very effective against all models as a single agent, and cyclophosphamide as a

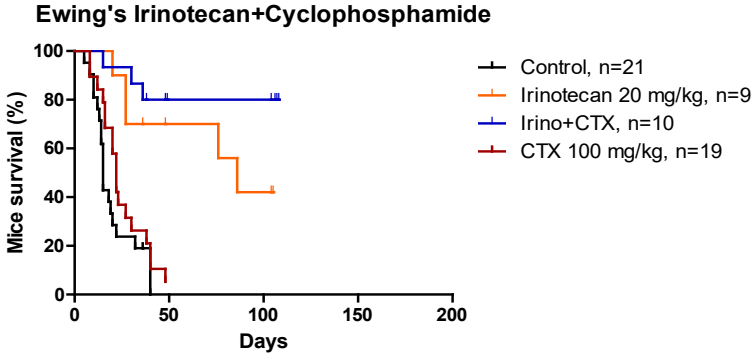
single agent was ineffective. The combination of MM-398 + CTX was more effective in maintaining mouse survival than MM-398 as a single agent.

Figure 5: MM-398 with and without cyclophosphamide is active against multi-drug resistant xenografts



The same models tested in Figure 5 were tested against the standard clinical formulation of irinotecan, alone and in combination with cyclophosphamide (CTX) (Figure 6).

Figure 6: Irinotecan with and without cyclophosphamide is active against multi-drug resistant xenografts



The current clinically employed irinotecan formulation was active as a single agent and in combination with CTX, but activity of the single agent was substantially lower than that seen with MM-398 as was activity of the combination**.**

MM-398, alone and in combination was also tested against multiple xenografts of neuroblastoma and rhabdomyosarcoma, in comparison with irinotecan in the current clinical formulation (with and w/o CTX). Activity was seen for MM-398 + cyclophosphamide against rhabdomyosarcoma xenografts (data not shown), the activity of MM-398 (alone or in combination with CTX) was modest compared to the activity observed in Ewing xenografts. Although the preclinical data with Ewing xenografts and MM-398 + cyclophosphamide was the most robust and encouraging of the data, as activity was observed in other pediatric solid tumors, and as both irinotecan and cyclophosphamide are active in recurrent neuroblastoma and rhabdomyosarcoma, most pediatric solid tumors are eligible for this phase I study.

4.0 OBJECTIVES

4.1 Primary Objective

To determine the Maximum Tolerated Dose (MTD) and safety of MM-398 in combination with cyclophosphamide in patients with recurrent or refractory pediatric solid tumors

4.2 Secondary Objectives

- To determine the pharmacokinetic properties of MM-398 in combination with cyclophosphamide in patients with recurrent or refractory pediatric solid tumors
- To measure time-to-event efficacy endpoints: progression-free survival (PFS) and time to treatment failure (TTF)
- To provide a preliminary assessment of responses in common pediatric solid tumors

4.3 Exploratory Objective

To explore biomarkers associated with toxicity and efficacy following treatment with MM-398 plus cyclophosphamide, specifically to obtain expression data for SLFN11 [54] in tumor tissue (whenever feasible) and to collect metabolic genotype information (e.g., UGT1A1 genotypes).

5.0 STUDY DESIGN

This is 3+3 dose escalating phase 1 study of MM-398 with cyclophosphamide in patients with recurrent or refractory pediatric solid tumors

All patients will participate in up to 28 days of screening, during which they will be assessed for eligibility and screened for the UGT1A1*1 and *28 allele.

Intravenous Cyclophosphamide Dosing

All patients will receive cyclophosphamide 250 mg/m^2 intravenously (given over 30 minutes) daily for 5 days.

MM-398 Dosing

The starting MM-398 dose (Dose Level 1) will be 60 mg/m^2 A Level 1A (30 mg/m^2) will enable dose de-escalation if 2 DLT's are observed at dose level 1. MM-398 will be administered intravenously over 90 minutes on the third day of the 5 day course of cyclophosphamide.

The MM-398 + cyclophosphamide regimen will be administered every 3 weeks, unless precluded by progressive disease (radiologic or clinical deterioration) or unacceptable toxicity.

The MM-398 will be dose-escalated as follows:

Dose Level	
1A	30 mg/m^2
1	60 mg/m^2
2	90 mg/m^2
3	120 mg/m^2
4	150 mg/m^2
5	180 mg/m^2
6	210 mg/m^2

Subjects will be enrolled in cohorts of 3 for each dose level. Dose escalation will proceed between each cohort and no intrapatient dose escalation will be allowed. DLT's will only be evaluated during cycle #1 of therapy for dose escalation purposes. Any DLT's and SAE's which occur in subsequent courses need to be reported, and will impact the individual patient, however, only those which occur in the first cycle of therapy for a given patient count toward dose escalation rules. If none of the first 3 subjects experiences DLT during their first cycle of therapy, then dose escalation will proceed with the next cohort of 3 patients. If 1 of 3 subjects develops DLT, the cohort will be expanded to 6 subjects. If no more than 1 subject of the 6 experience DLT, then escalation to the next dose level will proceed. If 2 subjects in any dose level subjects experience DLT, the dose escalation will be stopped and the prior dose level declared the MTD. A minimum of 6 evaluable subjects will be treated at the MTD dose level and no more than one of the 6 subjects may experience DLT at this dose level. The MTD will be considered as the recommended dose for future studies.

Dose level 6 entered 6 patients with one DLT, and as this is the maximal dose planned in this study, dose level 6 will be the dose for the expansion cohorts of up to 12 patients total of each histology (Ewing sarcoma, osteosarcoma, neuroblastoma, and rhabdomyosarcoma) which demonstrated an objective response in the dose escalation phase) will be enrolled. UGT1A1 *1 and *28 will be assessed as part of the screening/enrollment process. If a subject is found to be homozygous for the UGT1A1 *1 or *28 allele, they will be enrolled on dose level 3 (3 dose levels below starting dose). Individuals homozygous for the UGT1A1*1 or *28 allele (UGT1A1 7/7 genotype) may have increased risk of toxicity from MM-398. If a subject is found to be heterozygous, they will be entered on dose level 5 as a precaution. Only subjects with no variants will be enrolled on dose level 6. Additionally, patients with platelet counts between 100,000 and 150,000 will be enrolled on dose level 5 given concerns these patients have some baseline marrow toxicity at enrollment and maybe more likely to have worsening toxicity on study.

In light of the robust preclinical studies with MM-398 in Ewing sarcoma (which include a potential molecular marker of response for SN38 (SLFN11) shown to be highly expressed in Ewing tumors [54].) an expansion cohort of 12 patients with Ewing sarcoma will be accrued at the MTD to enable a more accurate determination of systemic toxicities, PK, and a preliminary assessment of activity for MM-398 in Ewing sarcoma. Should fewer than 6 Ewing sarcoma patients be entered onto the study at the MTD or the dose just prior to the MTD, than accrual of 12 Ewing sarcoma patients at the MTD will proceed, which is justified based on the preclinical and molecular marker of response data (in preclinical studies) for MM-398. In addition, if drug supplies are available, an expansion cohort of up to 12 patients will also be accrued and treated at the MTD. This expansion cohort will include histological types for which objective responses were observed or that have the potential to benefit from MM-398 therapy.

Tumor responses will be measured and recorded every 6 to 8 weeks using the RECIST guidelines (version 1.1). The local radiologist and/or PI assessment will determine disease progression.

CTCAE term (AE description) and grade

- The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- Any suspected or confirmed dose-limiting toxicity should be reported immediately (**within 48 hours**) to the Study Chair.

Definition of Dose-Limiting Toxicity (DLT)

- DLT will be defined as any of the following events that are possibly, probably or definitely attributable to the combination of MM-398 and cyclophosphamide. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

Non-hematological dose-limiting toxicity

- Any Grade 3 or higher non-hematological toxicity attributable to the investigational regimen with the specific exclusion of:
    - Grade 3 nausea and vomiting ≤ 3 days duration
    - Grade 3 diarrhea ≤3 days duration
    - Grade 3 mucositis or stomatitis ≤3 days duration
    - Grade 3 liver enzyme elevation, including ALT/AST/GGT, that returns to baseline within 7 days. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
    - Grade 3 fever
    - Grade 3 infection

- Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.
- Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

Hematological dose limiting toxicity is defined as:

- Grade 4 neutropenia for > 7 days
- Grade 4 thrombocytopenia on 2 separate days or thrombocytopenia requiring platelet transfusion on 2 separate days during cycle 1
- Thrombocytopenia with bleeding
- Myelosuppression that causes a delay of >14 days between treatment cycles.

Grade 3-4 febrile neutropenia will not be considered a dose-limiting toxicity.

If a subject experiences a dose-limiting toxicity, the subject should receive subsequent cycles at the next lower dose level.

5.1 Study Closure

The study will be stopped for any of the following reasons:

- More than 2 patients in the cohort of patients treated at the lowest planned dose level, 30 mg/m^2, experience DLT
- Significant safety concerns combined with a lack of activity is detected through adverse event reporting
- An expansion cohort of 12 patients with Ewing sarcoma will be accrued at the MTD. An expansion cohort of 12 patients will also be accrued for other histological types for which objective responses are observed

6.0 PATIENT SELECTION AND DISCONTINUATION

6.1 Number of Patients

There will be approximately 60 subjects enrolled across all participating institutions, depending on MTD dose level.

6.2 Patient Reservation

Investigators should consult the SPOC Operations Center to determine if the study is currently open for accrual before approaching participants for participation. Before enrolling a patient on study, a reservation must be made with the SPOC Operations Center. In order to make a reservation, you may call (806)-743-2690 or send an email to amanda.knight@ttuhsc.edu with the following information: (If sending an email, please put "Reservation Request" in the subject line)

- Study for which you want to make the reservation
- Name of the institution requesting reservation with contact information
- Patient Initials (Last, First)
- Patient date of birth

If an enrollment slot is available, you will receive a confirmation email or phone call, confirming your reservation. All reservations are good for 5 full calendar days starting with the next full day after the day the reservation is made.

6.3 Enrollment

Patients must be enrolled prior to beginning treatment on this study. Patients will be enrolled by contacting the SPOC Operations Center at Texas Tech University Health Sciences Center School of Medicine Cancer Center, Monday through Friday, 8:30 am-5:00 pm Central Time at (806)-743-2690 except holidays. You will be asked to complete the eligibility form provided in the protocol prior to making your call. In addition, the supporting documentation which confirms eligibility should be faxed to the SPOC Operations Office at (806)-743-2691 or emailed to amanda.knight@ttuhsc.edu.

Each patient will be assigned a unique SPOC registration and study subject number. The dose level of nanoliposomal irinotecan will be assigned by the SPOC Operations Center at the time of study registration. An email confirming eligibility and assigned dose level will be sent to the treating facility, Study Chair, and Study Vice-Chair. Patients should begin treatment within 3 calendar days of study enrollment.

Contact Person: Amanda Knight, RN, BSN, CCRP
SPOC Operations Center

TTUHSC SOM Cancer Center
3601 4th Street, STOP 9440
Lubbock, TX 79430-9440
Phone: (806)-743-2690
Fax: (806)-743-2691
Email: amanda.knight@ttuhsc.edu

6.4 Inclusion Criteria

The eligibility criteria listed below are interpreted literally and cannot be waived. All laboratory tests done to confirm eligibility must be performed within 1 week prior to enrollment. Disease evaluations must be done within 2 weeks of enrollment.

Inclusion criteria

6.4.1 Age

- Patients must be >12 months and <21 years of age at the time of study enrollment.

6.4.2 Diagnosis

- Patients with first or greater relapse or progression of Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, or osteogeneic sarcoma. Patients must have had histologic verification of malignancy at original diagnosis or relapse.
- Documented metastatic disease or unresectable disease at recurrence or progression, or documented disease progression after prior therapy in locally advanced or metastatic setting
- Disease Status: Patients must have either measurable or evaluable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria from the NCI for assessment of radiographic response.
- Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
- Patients with CNS disease are eligible. Although the potential of MM-398 crossing the blood-brain barrier is unknown, patients with brain metastases who meet all other eligibility criteria are eligible

6.4.3 Performance Status

- Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age. Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. (See Appendix II for Performance Scales)

6.4.4 Laboratory Assessments

Adequate Bone Marrow Function Defined as:

- For patients with solid tumors without known bone marrow involvement:
    - Peripheral absolute neutrophil count (ANC) ≥ 1000/mm3

  - Platelet count ≥ 100,000/mm3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment). If a subject has a platelet count < LLN (150,000/mm3), they will begin on dose level 5. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the platelet counts following transfusion, however they will not be eligible for assessment of hematologic toxicity
- For patients with known bone marrow involvement:
  - Patients with cytopenias secondary to known bone marrow involvement are eligible regardless of ANC or platelet counts
  - Patients may be enrolled and receive transfusions provided they are not known to be refractory to red cell or platelet transfusions. Patients with bone marrow involvement will not be evaluated for hematologic toxicity regardless of ANC or platelet counts at the time of diagnosis. At least 5 of every cohort of 6 patients with a solid tumor or CNS tumor must be evaluable for hematologic toxicity. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

- UGTA1A*1 and *28 allele genotype needs to be determined by the treating institution submitting a blood sample to Mayo Clinic BioPharma Diagnostics. Instructions for the sample collection will be provided to the sites. Results are required to begin therapy unless subject must begin therapy due to disease burden and study PI approval prior to result receipt. In these cases, the subject will begin therapy at dose level 3 until UGT1A1 results received, then the subject will be allowed to escalate to dose level 6 if results do NOT show a UGT1A1variant. If the results show a heterozygous polymorphism, the subject will start on dose level 5.

Adequate hepatic function as evidenced by:
- Direct Bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin > 2 g/dL

Adequate renal function as evidenced by:
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

6.4.5 Reproductive Function

- Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed prior to enrollment
- Both male and female patients of reproductive potential must agree to use a reliable method of birth control during the study and for 3 months following the last dose of study drug.

6.4.6 Previous Therapy

- Patients must have fully recovered from the acute toxic effects of all prior anticancer chemotherapy.
- Myelosuppressive chemotherapy: Patients must not have received myelosuppressive therapy within 3weeks of enrollment onto this study.
- Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
- Biologic (anti-neoplastic agent): At least 7 days after the last of a biologic agent that is not a monoclonal antibody and enrollment on this study. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
- Immunotherapy: At least 6 weeks since the completion of any type of immunotherapy, e.g. tumor vaccines.
- Monoclonal antibodies: At least 3 half-lives must have elapsed after treatment with a monoclonal antibody and enrollment on this study.
- XRT: ≥2 weeks must have elapsed for local palliative XRT (small port) and enrollment on study. At least 24 weeks must have elapsed since radiation if prior Total Body Irradiation (TBI), craniospinal XRT or if radiation to ≥50% radiation of pelvis has been administered. ≥ 42 days (6 weeks) must have elapsed if the patient has received other substantial BM radiation.
- Stem Cell Infusion without TBI: The patient must have no evidence of active graft vs. host disease, and ≥12 weeks must have elapsed since transplant or stem cell infusion and enrollment on this study.
- Prior treatment with irinotecan, topotecan, or cyclophosphamide as single agents or in combination are eligible for this study.

6.5 Exclusion Criteria

Patients must meet all of the inclusion criteria above and have none of the following exclusion criteria:

6.5.1 Clinical significant gastrointestinal disorders

- Patients must not have a clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1

6.5.2 Secondary malignancy

- Patients should not have a history of any second malignancy in the last 5 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Subjects with other malignancies are eligible if they have been continuously disease free
- for at least 5 years.

6.5.3 Cardiac function

- Patients cannot be diagnosed with NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled hypertension

6.5.4 Infection

- Patients who have an uncontrolled infection are not eligible.

6.5.5 Allergies

- Known hypersensitivity to any of the components of MM-398 or other liposomal products or patients with history of allergic reactions attributed to compounds of similar composition to irinotecan, or cyclophosphamide are not eligible.

6.5.6 Previous therapy

- Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half- lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study

6.5.7 Other Conditions

- Any other medical or social condition deemed by the investigator likely to interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results as appropriate to age

6.5.8 Reproduction

- Pregnant or breastfeeding females will not be allowed to participate in this study. Female patients with infants must agree not to breastfeed their infants while on study.

6.6 Discontinuations

6.6.1 Discontinuation of Patients

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol violation or deviation as defined in section 7.6, noncompliance, adverse event).

Criteria for Removal from Protocol Therapy

- Disease recurrence following complete remission
- Progressive disease while on study
- Refusal of further protocol therapy by patient/parent/guardian.
- Physician determines it is in patient's best interest
- Development of a second malignancy
- Adverse Event/Side Effects/Complications

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations until the originally planned cycle end date or until all adverse events attributable to study treatment have resolved, whichever happens later. The only exception is with documentation of withdrawal of consent.

Patients who come off protocol therapy after cycle 1 are to be followed every 3 months after their last study visit, for event free survival and overall survival status, until they meet the criteria for Off Study as indicated below. Adverse events should be followed through resolution, where possible. Adverse events that are ongoing at the time of treatment discontinuation should be followed through the 30-day follow-up visit.

Off Study Criteria

- Death
- Lost to follow-up
- Enrollment onto another trial with tumor therapeutic intent
- Withdrawal of consent for any further data submission
- 2 year anniversary of the date the patient completed therapy on this study

6.6.2 Discontinuation of Study Sites

A study site may choose to withdraw participation in the study at any time for any reason. Similarly, the investigator and/or sponsor can discontinue or disqualify a study site at any time for any reason (protocol violation or deviation).

6.6.3 Discontinuation of the Study

The study will be stopped for any of the following reasons:

- More than 2 patients in the cohort of patients treated at the lowest planned dose level, 30 mg/m2, experience DLT
- Safety concerns or lack of activity is detected through adverse event reporting

An expansion cohort of 12 patients with Ewing sarcoma will be accrued at the MTD. An expansion cohort of 12 patients will also be accrued for other histological types for which objective responses are observed.

7.0 INVESTIGATIONAL PRODUCT AND STUDY TREATMENT

7.1 Method of Assigning Patients to Treatment Groups

Patient assignment to treatment groups is non-random and is open label (See 5.0 Study Design)

7.2 Description of MM-398 (nanoliposomal irinotecan = Onivyde)

MM-398 is irinotecan (also known as CPT-11) encapsulated in a liposome drug delivery system (irinotecan sucrosofate liposome injection). It will be supplied in sterile, single-use vials containing 9.5 mL of MM-398 at a concentration of 4.3 mg/ml. The vials contain a 0.5 mL excess to facilitate the withdrawal of the label amount from each 10 mL vial.

7.2.1 Storage and Handling of MM-398

MM-398 must be stored refrigerated (2 to 8ºC, 36 to 46ºF) with protection from light. The product must *not* be frozen. Freezing will disrupt the liposome structure and result in the release of free irinotecan. MM-398 must be diluted prior to administration. Because of possible microbial

contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2º to 8ºC) or within 6 hours if kept at room temperature (15º to 30ºC).

7.2.2 Packaging and Labeling of MM-398

MM-398 will be provided by Ipsen Pharmaceuticals and labeled in accordance with local regulatory requirements.

7.2.3 Doses and Administration of MM-398

Prior to administration, MM-398 must be diluted in 5% Dextrose Injection solution (D5W) to a suitable volume for infusion to a final concentration of 0.2 to 2.0 mg/mL. The dose of MM-398 to be administered will be calculated using the patient's body surface area (BSA). MM-398 must be diluted in the highest tolerated volume for each patient in order to decrease the probability of infusion reactions. The final volume containing the planned dose should be appropriate for safe administration to the child over 90 minutes. MM-398 can be administered using standard PVC containing intravenous administration bags and tubing. Syringe pumps may be used for small infusion volumes. Care should be taken not to use inline filters or any diluents other than D5W. See 5.0 Study Design for additional details on dosing.

7.2.4 Premedication

All patients should be premedicated prior to MM-398 infusion with standard doses of dexamethasone and a 5-HT3 antagonist or other anti-emetics as per standard institutional practices for irinotecan administration. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles. Antibiotics may be given prior to MM-398 for patients who experience grade 3-4 GI toxicities. See Appendix III for guidelines.

Pre and post-hydration as well as monitoring urine output during cyclophosphamide administration should be performed based on institutional guidelines but may include:

- Prior to start of cyclophosphamide
  - Fluid bolus of 20 ml/kg NS over 30 minutes
  - Prehydration with D5W/0.45% NaCl at 125 mL/m²/hour until specific gravity ≤ 1.010
- Antiemetic therapy
  - Dexamethasone 5 mg/m2 IV
  - Ondansetron 0.45 mg/kg IV (maximum dose 16 mg)
- Cyclophosphamide 250mg/m2 IV over 30 minutes
- During cyclophosphamide
  - Monitoring for adequate urine output.
  - Diuretics (eg, furosemide) may be used to increase urine output.
  - Mesna is not generally required for this dose of cyclophosphamide, but may be administered at institutional discretion.
- Following cyclophosphamide,
  - Post-hydration with D5W/0.45% NaCl at 125 mL/m²/hour for 2 hours
- MM-398 is given IV over 90 minutes on day 3 only

7.3 Treatment Considerations with MM-398

The long circulating pharmacokinetics, high intravascular drug retention in the liposomes, and enhanced permeability and retention (EPR) effect may potentially result in site-specific drug delivery to solid tumors and therefore the local bioactivation is hypothesized to result in reduced exposure to potential sites of toxicity and increased exposure to neighboring cancer cells within the tumor. However, it is theoretically possible that the side effect profile may differ from native irinotecan.

7.3.1 MM-398 Dose Modifications

Dose modifications for diarrhea. See Appendix III for specific guidelines for supportive care measures for patients who develop therapy-associated diarrhea.

- If dose-limiting Grade 3 (> 3 days) or Grade 4 therapy-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications and appropriate use of prophylactic antibiotics, the dose of MM-398 should be reduced to the next lowest dose level for subsequent cycles.

- If dose-limiting Grade 3 (> 3 days) or Grade 4 diarrhea is documented despite maximal use of anti-diarrheals, prophylactic antibiotics, and the dose reductions, the patient should come off protocol therapy.

Definition of Dose-Limiting Toxicity (DLT)

- DLT will be defined as any of the following events that are possibly, probably or definitely attributable to the combination of MM-398 and cyclophosphamide. The DLT observation period for the purposes of dose-escalation will be the <u>first cycle of therapy</u>.

Dose limiting hematological and non-hematological toxicities are defined differently.

Non-hematological dose-limiting toxicity

- Any Grade 3 or higher non-hematological toxicity attributable to the investigational regimen with the specific exclusion of:
    - Grade 3 nausea and vomiting < 3 days duration
    - Grade 3 diarrhea ≤3 days duration
    - Grade 3 mucositis or stomatitis ≤3 days duration
    - Grade 3 liver enzyme elevation, including ALT/AST/GGT, that returns to baseline within 7 days Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
    - Grade 3 fever
    - Grade 3 infection

- Non-hematological toxicity that causes a delay of <u>≥</u> 14 days between treatment cycles.
- Allergic reactions that necessitate discontinuation of study drug <u>will not</u> be considered a dose-limiting toxicity.

Hematological dose limiting toxicity is defined as:

- Grade 4 neutropenia for > 7 days

- Grade 4 thrombocytopenia on 2 separate days or thrombocytopenia requiring platelet transfusion on 2 separate days during cycle 1. Thrombocytopenia with bleeding
- Myelosuppression that causes a delay of >14 days between treatment cycles.

Grade 3-4 febrile neutropenia will not be considered a dose-limiting toxicity.

7.3.2 Management of Infusion Reactions

Therapy modifications for patients who develop infusional reactions to MM-398 should be:

Grade	Action
Grade 1: Transient flushing or rash, drug fever < 38◦ C (<100.4 ◦ F) And Grade 2: Rash, flushing, urticaria, dyspnea, drug fever ≥ 38◦ C (≥100.4 ◦ F)	• If a patient develops a hypersensitivity reaction, stop the infusion and wait 30 to 60 minutes (depending upon the reaction severity). At the physician's discretion, it may be possible to resume treatment by administering the medication at a slower rate (over 120 minutes), by premedicating with diphenhydramine or an H2 blocker. If an H2 blocker is used, the manufacturer recommends famotidine 0.5 mg/kg IV maximum dose 20 mg, rather than cimetidine, because it lacks reported drug interactions. If famotidine is unavailable, administer ranitidine 1-2 mg/kg IV maximum dose 50 mg. • If grade 1-2 infusion reactions recur with subsequent dose, add dexamethasone 0.2 mg/kg (max 10mg) IV or equivalent to premedications above. (Only dose interruption/discontinuation, but not dose reduction is required for allergic/infusional reactions
Grade 3: Symptomatic bronchospasm with or without urticaria, allergy-related edema/angioedema, hypotension	• Stop infusion immediately and remove the infusion tube • Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2mg/kg (max 10mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Hospital admission should be considered. • Discontinue MM-398 treatment
Grade 4: Anaphylaxis	• Stop infusion immediately and remove the infusion tube • Administer diphenhydramine hydrochloride 1 mg/kg (max 50mg) IV, dexamethasone 0.2 mg/kg (max 10mg) IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated • Discontinue MM-398 treatment

7.3.3 MM-398 Dose Modifications for Hematological Toxicities

Patients who have dose-limiting thrombocytopenia should receive subsequent cycles at the next lower dose level. Retreatment at these lower doses should be initiated when criteria described in Section 6.4.4 are met.

Patients may receive prophylactic myeloid growth factor support in the first cycle of therapy. If dose-limiting neutropenia occurs after myeloid growth factor support is added, patients should receive subsequent cycles at the next lower dose level.

Patients who experience dose-limiting hematological toxicity after dose reductions described above must be removed from protocol therapy.

Patients who have a dose-limiting hematological toxicity that does not resolve to baseline within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

7.3.4 MM-398 Dose Modifications for Non-Hematological Toxicities

- If the dose-limiting toxicity is a non-hematological toxicity other than those specifically listed above, subsequent cycles of therapy should be administered at the next lower dose level.

- If non-hematological dose-limiting toxicity recurs at the reduced dose, the patient must be removed from protocol therapy.

- Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline within 21 days after the planned start of the next treatment cycle (unless otherwise specified above) must be removed from protocol therapy.

If a subject experiences a dose-limiting toxicity, the subject should receive subsequent cycles at the next lower dose level.

7.3.5 Pregnancy

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to an effective contraceptive method.

7.4 Concomitant Therapy

7.4.1 Antiemetic Therapy

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary.

7.4.2 Colony Stimulating Factors

Growth factors that support white cell number or function may be administered following the first cycle of therapy. Growth factors should be administered in all cycles in accordance with Section 7.3.3. In addition, growth factors may be administered to patients with culture proven bacteremia or proven or suspected invasive fungal infection.

7.4.3 Other Treatments

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Use of prophylactic antimicrobials to prevent pneumocystis pneumonia is required.

7.5 Prohibited Therapy

Concurrent cancer therapy, including chemotherapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug during the first 4 cycles of therapy. If these treatments are administered the patient will be removed from protocol therapy. Similarly, no other investigational agents may be given while the patient is on study.

Radiation therapy is prohibited during the first 4 cycles of therapy but may be administered following cycle 4. The indication (for example, local control of a metastatic site) and radiation field and dosing should be communicated with to study chair. Patients who receive radiation after cycle 4 will be allowed to remain on study.

7.6 Drug Ordering Information

MM-398 will be provided by Ipsen Pharmaceuticals.

7.7 Accountability of Study Drug

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs. The NCI Drug Accountability Record Form (DARF) or another suitable alternative may be used for this purpose.

7.8 Cyclophosphamide (Cytoxan)

Source and Pharmacology: Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P-450 isoenzymes (CYP2B6, CYP2C9 and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. Cyclophosphamide is well absorbed orally with a bioavailability greater than 75%. The plasma half-life ranges from 4.1 to 16 hours after IV administration and 1.3 to 6.8 hours after oral administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy, excluding the above conditions	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1] *Dependent on dose, age, gender, and degree of pubertal development at time of treatment*
[2] *Risk increased with pulmonary chest irradiation and higher doses*
(L) Toxicity may also occur later

Formulation and Stability:

Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 gm and 2 gm vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30º C (86ºF).

Guidelines for Administration:

Cyclophosphamide for Injection: Reconstitute with sterile water or Bacteriostatic water for injection (paraben preserved only) to a concentration of 20 mg/mL. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. If administered as undiluted drug at the 20 mg/ml concentration, reconstitute with NS only to avoid a hypotonic solution. Cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

Patients are to receive appropriate antiemetic therapy as well as pre and post-hydration and monitoring of urine output based on institutional guidelines (see section 7.2.4). Intravenous cyclophosphamide is administered at 250 mg/m^2 over 30 minutes and is given daily for 5 days, days 1-5 of each cycle, every 3 weeks (21 days) until progressive disease (radiologic or clinical deterioration) or unacceptable toxicity.

Supplier: Commercially available from various manufacturers. See package insert for further information.

7.9 MM-398

Source and Pharmacology:
MM-398 (also known as Onivyde) is irinotecan (also known as CPT-11) encapsulated in a nanoliposome drug delivery system (irinotecan sucrosofate liposome injection). The active ingredient of MM-398 injection is irinotecan, as the sucrose octasulfate salt. Irinotecan is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble analog of the naturally-occurring alkaloid, camptothecin. Topoisomerase I inhibitors work to arrest uncontrolled cell growth by preventing the unwinding of DNA and therefore preventing replication. The pharmacology of CPT-11 is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug [8, 9, 10]. CPT-11 is a prodrug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38 [11]. SN-38 is cleared via glucuronidation, for which major pharmacogenetic differences have been shown, and biliary excretion. These drug properties contribute to the marked heterogeneities in efficacy and toxicity observed clinically with CPT-11 [12, 13]. Hence, drug carrier technologies represent a rational strategy to improve the pharmacokinetics and biodistribution of CPT-11 while protecting it from premature metabolism.

MM-398 employs a novel intraliposomal drug stabilization technology for encapsulation of irinotecan into long-circulating liposome-based nanoparticles with high drug load and high in vivo stability.

The stable nanoliposome formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release should improve activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the more sensitive S-phase of the cell cycle. The long circulating pharmacokinetics, high intravascular drug retention in the liposomes, and enhanced permeability and retention (EPR) effect may potentially result in site-specific drug delivery to solid tumors. Stromal targeting results from the subsequent depot effect, where liposomes accumulating in TAMs release the active drug and convert it locally to the substantially more cytotoxic SN-38. The preferentially local bioactivation should result in reduced exposure to potential sites of toxicity and increased exposure to neighboring cancer cells within the tumor. In addition, since SN-38 is not recognized by P-glycoprotein, a drug transporter that plays an important role in acquired drug resistance, MM-398 is likely to be active in tumors resistant to other standard chemotherapies.

8.0 STUDY PROCEDURES

8.1 Clinical Procedures

8.1.1 Medical History

Medical History including complete review of systems will be performed during screening and on day 1 and day 3 of each cycle. A medically appropriate review of systems will be performed prior to chemotherapy administration on subsequent days.

8.1.2 Physical Examination

Physical examinations will be performed during screening and on day 1 and 3 of each chemotherapy cycle. During Course 1, physical examinations will also be performed on days 8 and 15, and may be performed in future courses on day 8, 15 and/or additional days prior to chemotherapy as deemed medically appropriate. Physical examination findings at screening will be classified using standard categories as listed on the medical history CRFs. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline finding will be considered an adverse event, recorded on the adverse event CRF, and monitored

8.1.3 Vital Signs, Height, Weight, Body Surface Area

Vital signs will be measured daily prior to chemotherapy administration. Vital signs include the following:

- Heart rate
- Blood pressure
- Body temperature
- Respiratory rate

The same position and arm should be used each time vital signs are measured for a given patient. Any vital sign value that is judged by the investigator as a clinically significant change, worsening) compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored.

Body weight (kg) will be determined at screening, within 2 days prior to the first administration of study drug, and then according to the standard of care procedures at each study center. Height (cm) will be measured at screening only. BSA (m^2) will be calculated using a standard nomogram within 2 days prior to the first administration of study drug and at subsequent visits if the patient experiences more than a 10% change in actual body weight from the weight used for the most recent BSA calculation.

8.1.4 Performance Score

Karnofsky (for patients older than 16 years of age at screening) or Lansky (for patients 16 years of age or younger at screening) performance status will be assessed at screening, on days 1 and 15 of induction treatment, and on day 1 of subsequent treatment cycles. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. The scale used at screening will be used throughout the study.

8.1.5 Disease Assessment

Imaging studies must be obtained within 2 weeks prior to start of chemotherapy (repeat the tumor imaging if necessary). For patients whose disease is evaluated with a bone marrow biopsy, the bone marrow aspirates and biopsies are required within 2 weeks prior to start of chemotherapy.

Tumor Disease Evaluation should be obtained after cycles 2 and 4. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt

not to confirm this finding radiographically. Patients who have stable disease or better after two disease evaluations can undergo repeat disease reevaluations after every 3rd cycle of treatment.

Response Criteria for Patients with Solid Tumors
This study will use the (RECIST) Response Evaluation Criteria in Solid Tumors from the NCI for assessment of radiographic response.

Measurable Disease
The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 20 mm. With spiral CT scan, lesions must be at least 10 mm. The investigator will identify up to 10 measurable lesions to be followed for response. Serial measurements of lesions are to be done with appropriate imaging modalities. Bone scans cannot be used to measure lesions. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

Quantification of Disease Burden
The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

End-of-Cycle Response

- Complete Response (CR): Disappearance of all target and non-target lesions. If immunocytology is available, no disease must be detected by that methodology.

- Partial Response (PR): At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

- Progressive Disease (PD): An increase of at least 20% in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions, or evidence of laboratory or clinical progression.

Overall Best Response Assessment:
Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect.

Response Criteria for Patients with Solid Tumors and Evaluable Disease

- Evaluable Disease: The presence of at least one lesion with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques (including MIBG, PET scan, immunocytochemistry techniques, tumor markers or other reliable measures.)

- Complete Response (CR): Disappearance of all evaluable disease.

- Partial Response (PR): Partial responses cannot be determined in patients with evaluable disease

- Stable Disease (SD): That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

- Progressive Disease (PD): The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

Overall Best Response Assessment:
Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect.

Best Response
At least two overall response assessments on two consecutive determinations, separated by at least a 3-week time period, are required to determine the patient's Best Response. Two overall response assessments of CR before progression are required for best response of CR. Two overall response assessments of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two overall response assessments of stable disease or better before progression, but not qualifying as CR or PR, are required for a best response of stable disease; if the first overall response assessment is unknown, only one such determination is required. Patients with an overall response assessment of PD or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all overall response assessments after the first determination and before progression are unknown.

Table 6. Sequences of overall response assessments with corresponding best response.

1st Assessment (after cycle	2nd Assessment	3rd Assessment	Best Response
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

8.2 Laboratory Procedures

All clinical laboratory test results outside of the reference range will be interpreted by the investigator using the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening

A laboratory test result that has significantly worsened (according to medical judgment) compared with the baseline result will be recorded on the CRF as an adverse event and monitored. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or requires medical treatment or further diagnostic work-up. Clinical laboratory tests will be performed using local laboratories. Specific laboratory tests to be performed are listed below.

8.2.1 Complete Blood Count

The following hematology tests will be performed:

- white blood cell (WBC) count and differential count
- absolute neutrophil count (ANC)
- hemoglobin
- platelet count

8.2.2 Serum Chemistry

The following serum chemistry tests will be performed:

- sodium
- potassium
- chloride
- bicarbonate or carbon dioxide
- blood urea nitrogen (BUN)
- creatinine
- glucose
- calcium
- alanine aminotransferase (ALT)
- Total and direct bilirubin

8.2.3 Pregnancy Test

Beta human chorionic gonadotropin (ßHCG) serum tests or human chorionic gonadotrophin (HCG) urine tests will be performed for all women of childbearing potential at screening and if clinically indicated thereafter. Any patient becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol. All patients who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age) will be reported to the sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.

*8.2.4 UGT1A1*28 Allele*

- UGTAIA*28 allele must be assessed by Mayo Clinic BioPharma Diagnostics during screening and results will be reported to SPOC Operations Office as soon as available. Results are required to begin therapy unless subject must begin therapy due to disease burden and study PI approval prior to result receipt. In these cases, the subject will begin therapy at dose level 3 until UGT1A1 results received, then the subject will be allowed to escalate to dose level 6 if results do NOT show UGT1A1 variant. If the results show a heterozygous polymorphism, the subject will start on dose level 5.

8.2.5 Pharmacokinetic Assessments

All patients will undergo MM-398 drug plasma level measurements during and after Course One to determine the pharmacokinetics of the study drug. PK samples will be drawn on Days 3, 4, 5, 8, and 10 at the following timepoints: pre-MM-398 infusion, and within 4 hrs, 24 hrs, 48 hrs, 120 hrs, and 168 hrs post-infusion (the 168 hr sample is optional).

For patients with double-lumen Hickman or double-lumen PICC catheters only: at the time of the blood draw, the i.v. tubing should be completely flushed with at least twice as much normal saline as the estimated void volume in the tubing (i.e. flush with at least 15-20 cc of normal saline for > 12 kg patient). The pharmacokinetic blood specimen should be drawn from the OPPOSITE lumen, discarding the first few cc's of blood per routine. This precaution is needed to prevent entrainment of the study drug for the tip of infusion lumen (even if infusion is turned off) into the blood sample taken from the opposite lumen.

For patients with a port-a-cath (single or double lumen) or single lumen catheters (including but not limited to Broviac, PICC, and Hickman): a peripheral catheter kept open with sterile isotonic saline, or heparin flush, should be placed prior to the start of drug administration on Day 0 to collect the blood specimens, and replaced as needed. This precaution is necessary because 1) complete flushing of the port-a-cath reservoir is less certain and therefore entrainment more likely and 2) drug may adhere to the line of a single lumen catheter and become entrained when the blood sample is withdrawn. For patients with peripheral saline or heparin locks placed for blood sampling, sufficient blood must be withdrawn and discarded to clear the void volume of the saline lock. The blood sample for analysis should then be drawn and the lock reflushed with sterile saline or heparin. In all other circumstances, PK samples should be obtained by peripheral venipuncture.

In the expansion cohort, patients are tested for the status of UGT1A1 polymorphism. For the patients without the polymorphism, the collection of PK samples is optional. In the patients with a homozygous or heterozygous polymorphism, PK samples will be drawn on Days 3, 4, 5, 8, and 10 at the following timepoints: pre-MM-398 infusion, and within 4 hrs, 24 hrs, 48 hrs, 120 hrs, and 168 hrs post-infusion (the 168 hr sample on Day 10 is optional).

Minimum volume required:	2 ml of blood in a green top (heparinized) tube
Collection time points: NOTE: Patients with double lumen Hickman and double lumen PICC lines may have PK samples drawn from the second lumen of their lines if sample is drawn as described above. All other patients should have a peripheral catheter saline or heparin	For the FIRST COURSE of the study drug, blood samples are drawn at the following times relative to MM-398 infusion: A pre-infusion blood sample (labeled Time=0) should be drawn, then additional samples post-infusion: within 4 hours, 24 hours, 48 hours, 120 hours, and 168 hours (the 168 hr sample is optional). PK samples will only be obtained in Course One.

lock placed for serial blood sampling.	
Specimen Processing:	**Place each sample on ice** and send to lab for immediate processing. Plasma should be separated by low speed centrifugation (1500 rpm for 10 min), transferred to a well-labeled polypropylene tube, and frozen immediately at -70ºC. Forward samples on dry ice to the lab of Dr. Min Kang at TTUHSC.
Specimen Labeling:	Each tube must be labeled with SPOC registration number, study ID number, and the DATE and TIME the specimen was drawn. Please indicate the hour from start of infusion at which the sample was drawn, if available.
Specimen Packaging and Shipping:	Send plasma samples, preferably batched, WITHIN ONE MONTH OF OBTAINING SAMPLES ON DRY ICE via overnight Federal Express, Monday through Thursday to: Dr. Min Kang c/o Cancer Center Core Labs Texas Tech University Health Sciences Center 3601 4th Street, STOP 9450 Lubbock, TX 79430-9450 Kang office phone: 806-743-2694 Core Lab phone: 806-743-2707 Core Lab Contact Person: Kristyn McCoy or Jonas Nance, kristyn.mccoy@ttuhsc.edu or jonas.nance@ttuhsc.edu Laboratory phone: (806)-743-2707. Please include completed Specimen Transmittal Form with shipment and FAX a copy to SPOC Operations Center (806)-743-2691. Please notify Amanda Knight amanda.knight@ttuhsc.edu before shipping specimens. If there are questions or problems with the samples, please call the SPOC Operations Center, or Dr. Min Kang at 806-743-2694. Please use the following FedEx Account# 4370-3390-0. **Also, please email or call the laboratory personnel or Dr. Min Kang when specimens are shipped.**

8.2.6 Assessing SLFN11 expression in tumor cells.

Recent data suggest that high expression of SLFN11 may be associated with a high degree of cytotoxic response to topoisomerase inhibitors [54]. Thus, an exploratory aim of this protocol that is *strongly encouraged* is to submit frozen tumor tissue for analysis of SLFN11 expression, which will be carried out in Dr. Kang's laboratory by RT-PCR. While tumor biopsies obtained close to time of entry onto this protocol are preferred, frozen tumor from earlier in the patient's course of therapy would also be valuable for assessing SLFN11 expression. If no tumor is available but tumor (consented for research) was known to be submitted to a biobank, information on the

biobanked material should be provided so that requests for access to that material can be attempted. For patients with bone marrow involvement, it is requested that if feasible a 5 to 10 ml bone marrow aspirate (heparinized) be shipped to the resource lab as the lab will attempt to culture the tumor cells and also obtain mouse xenografts so as to provide a sample of tumor without undue marrow cell contamination that can be used for SLFN11 expression. Any samples submitted for this exploratory aim should be submitted to the PK lab as per the instructions in section 8.2.5. Frozen samples should be sent on dry ice, fresh marrow samples at ambient temperature but in a Styrofoam insulated container to prevent undue temperature changes, and in all cases by next day air service.

9.0 SCHEDULE OF ASSESSMENTS

History, Physical examination, CBC and serum chemistries will be performed according to the following schedule:

Day	Chemotherapy		Assessments
1	Cyclophosphamide		a, c, d
2	Cyclophosphamide		
3	Cyclophosphamide	MM-398	a, b, c
4	Cyclophosphamide		b
5	Cyclophosphamide		b
8			a, b, c
10			b (optional)
15			a, c
15-21	(prior to therapy)		e
22	Start next cycle		a, c, d
30-day follow-up visit			a, f

A cycle may be repeated every 21 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section

a) H&P; after Course One, physical exam is only required on days 1 and 3 (physical exam may be performed on additional days if indicated for good clinical care)
b) PK studies (cycle 1 only)
c) CBC with differential, serum chemistries
d) Pregnancy test
e) Response evaluation occur after cycles 2, 4, 7, 10 and after every third cycle thereafter.
f) After this visit, patients should continue to be followed every 3 months for event free survival and overall survival status via clinic visits, phone, email or mail.

10.0 ADVERSE EVENT REPORTING REQUIREMENTS

10.1 Definition

An adverse experience is defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific

criteria, and/or if the investigator considers them to be adverse events. The investigator will evaluate all adverse experiences as to their severity and relationship to the investigational product, MM-398, nanoliposomal irinotecan.

10.1.2 Unexpected Adverse Event

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in drug information section of the protocol.

10.1.3 Serious Adverse Events

Serious adverse events are to be collected from the time patient initiates protocol therapy until 30 days following discontinuation of study drug administration have elapsed.

A **serious** adverse experience is defined as follows:

Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (*e.g.,* sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An <u>important medical event</u> that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.2 Documenting Adverse Events

Adverse events and serious adverse events will be collected and reported on the case report forms (CRFs) beginning with the first dose of investigational product until 30 days following the last dose of nanoliposomal irinotecan, whether elicited or spontaneously reported by the patient. Adverse events should be followed through resolution, where possible. Adverse events that are ongoing at the time of treatment discontinuation should be followed through the 30-day follow-up assessment. Serious adverse events that occur after signing the study-specific informed consent and prior to the initial dose of study drug will also be collected only if the investigator believes the SAE to be a result of study participation. These SAEs will be collected until the first dose of study drug or until the patient has been documented as a study failure. Although pregnancy is not considered an adverse event or a serious adverse event, the any pregnancy will require collection of obstetrical history and labor/delivery records. All adverse events will be reported for at least 30 days following the last dose of nanoliposomal irinotecan, whether elicited or spontaneously reported by the patient.

10.3 Reporting Serious Adverse Events

Reporting requirements *may* include the following considerations:

- Whether the patient has received an investigational or commercial agent
- The characteristics of the adverse event including the *grade* (severity)
- The *relationship to the study therapy* (attribution)
- The *prior experience* (expectedness) of the adverse event
- The phase (1, 2, or 3) of the trial
- Whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. See section 13.6 for commercial agent reporting requirements.

10.4 Determining the Severity and Relatedness of Adverse Events

Step 1: **Identify the type of event using the NCI Common Toxicity Criteria (CTCAE), version 4.0.** The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page **(http://ctep.cancer.gov).** Additionally, if assistance is needed, the NCI has an index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: **Grade the event using the NCI CTCAE.**

Step 3: **Determine whether the adverse event is related to the protocol therapy** The investigator will assess the causal relationship between the investigational product and the adverse event. The investigator will use his/her clinical expertise and judgment to select

the attribution category below that best fits the circumstances of the AE. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Unrelated:

- The adverse event is *clearly unrelated* to the investigational agent(s).
- Does not follow a known response pattern to the suspect investigational product (if response pattern is previously known).
- Can be explained by the known characteristics of the subject's clinical state or therapy administered to the subject.

Unlikely:

- The adverse event is *doubtfully* related to the investigational agent(s).
- May or may not follow a reasonable temporal sequence from administration of the investigational product.
- Likely explained by the known characteristics of the subject's clinical state or other therapy administered to the subject.

Possibly Related:

- The adverse event *may be* related to the investigational agent(s).
- Follows a reasonable temporal sequence from administration of the investigational product.
- May also be reasonably explained by the subject's clinical state or therapy administered to the subject.
- May follow a known response pattern to the investigational product (if response pattern is previously known)

Probably Related:

- The adverse event *is likely* related to the investigational agent(s).
- Follows a reasonable temporal sequence from administration of the investigational product.
- May follow a known response pattern to the investigational product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable;

Definitely Related:

- The adverse event is *clearly related* to the investigational agent(s).
- Follows the temporal sequence from administration of the investigational product.
- Follows a known response pattern to the investigational product.
- Cannot be explained by the known characteristics of the subject's clinical state or other therapy administered to the subject.
- Is confirmed by improvement of symptoms on stopping or slowing administration of the investigational product and re-emergence of symptoms on restarting administration of the investigational product, (if applicable).

Step 4: **Determine the prior experience of the adverse event.** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes

only, when either the type of event or the severity of the event is not listed in the current specific protocol or when either the type of event or the severity of the event is not listed in the toxicities listed in the drug information section of the protocol.

Step 5: **Report the following adverse events in an expedited manner.**

- Grade 4 or 5 adverse events regardless of attribution.
- Report all Grade 3 events if they are possibly, probably or definitely related to administration

Step 6: Determine if the protocol treatment given prior to the adverse event included an investigational agent, a commercial agent, or a combination of investigational and commercial agents.

10.4.1 Reporting Methods for Investigational Agents (nanoliposomal irinotecan)

24-hour Notification

All serious adverse experience, including death due to any cause that occurs during this study must be reported to the SPOC Operations Center within 24 hours of becoming aware of the serious adverse experience. Notification should be made by either Telephone (806)-743-2507 or Email amanda.knight@ttuhsc.edu or cory.rosas@ttuhsc.edu and include the following information:

Patient SPOC Study ID
Serious Adverse Event Name
Serious Adverse Event Grade
Date Serious Adverse Event Occurred
Name and Phone Number of Physician in charge of the case
Name and Phone Number of CRA or Research nurse working with the study

Written Report

Submit a written Serious Adverse Event form via fax (806)-743-2691or email: amanda.knight@ttuhsc.edu or cory.rosas@ttuhsc.edu to the SPOC Operations Center within 5 working days of the event.

10.4.2 IND Sponsor Reporting Requirements

The SPOC Operations Center will contact the IND holder within 24 hours of learning of the event from the reporting site and will forward all written reports as soon as they are received.

Per CFR 312.32 (c), the investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any adverse experience **associated with use of the drug** that is **both serious and unexpected.** Each written notification shall be made as soon as possible, and in no event later than **15 calendar** days after the investigator sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A (MedWatch) or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". Follow-up information to a safety report should be submitted as soon as the relevant information is available.

The investigator-sponsor must also notify FDA **by telephone** or by **facsimile** transmission of any **unexpected fatal or life-threatening experience associated with use of the drug** in the clinical studies conducted under the IND as soon as possible but in no event later than **7 calendar** days after initial receipt of the information.

Each telephone call or facsimile transmission to the FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND; a specific contact person is assigned to each IND at the time the application is filed, and this will be included in the FDA's correspondence acknowledging receipt of the IND application.

Merrimack Pharmaceuticals or its' designee, usually the MM-398 medical monitor, will be copied on all safety related correspondence to the FDA.

10.5 Serious Adverse Event Reporting for Commercial Agents:

All serious adverse drug reactions for commercial agents should be reported within 24 hours to the SPOC Operations Center.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the following procedures should be followed:

10.5.1 What To Report

Any life-threatening (Grade 4) or fatal (Grade 5) adverse event with an attribution of possible, probable or definite to a study drug that is **also unexpected** (not listed in the package label).

10.5.2 When To Report

These events should be reported within five (5) working days to the SPOC Operations office using the Medwatch form. A copy of the Med Watch form can be obtained from the FDA's Med Watch Web site at www.fda.gov/medwatch .

10.5.3 Where To Report

Submit the completed Medwatch form to the SPOC Operations Center within 5 working days of the event via fax (806)-743-2691 or email: amanda.knight@ttuhsc.edu orcory.rosas@ttuhsc.edu. The serious adverse event will be reported to the FDA by the SPOC Operations Center.

11.0 DATA QUALITY ASSURANCE

The South Plains Oncology Consortium (SPOC) will monitor the study. SPOC has a Data Safety and Monitoring Committee (DSMC) that is comprised of oncologists who are not actively participating in SPOC clinical trials. The SPOC DSMC meets by teleconference to review any serious, unexpected adverse events on SPOC clinical trials. Serious adverse events are captured on case report forms and immediately transmitted to the SPOC Operations Center, which insures the IND Sponsor and Study Committee are aware of the event. As determined by the nature of the event, safety memos are generated and sent to participating institutions for submission to their

respective IRB's. In accordance with good clinical practices, all adverse events in a given cohort will be reviewed by the SPOC DSMC prior to all dose escalations. The SPOC DSMC will review all serious, unexpected adverse events in real time with other members of the DSMC by phone conference. Additionally, this trial will be monitored by the SPOC DSMC after the first patient, upon any dose de-escalations, or at least annually. Meeting minutes will document these reviews and will be made available as needed. A description of the SPOC DSMC is contained in the SPOC Standard Operating Procedure for the SPOC DSMC.

The handling of data, including data quality assurance, will comply with regulatory guidelines (e.g., ICH and GCP) and applicable SOPs and working instructions. Data management and control processes specific to this study will be described in a data management plan. All steps and actions taken regarding data management and quality assurance will be documented in a data handling report.

At the end of the study, the study data will be locked and the data will be released for reporting and statistical analysis.

12.0 STATISTICAL ANALYSES

12.1 Statistical Hypothesis and Sample Size

Up to 75 subjects will be enrolled, depending on the MTD level and possible expansion cohorts at the MTD. Subjects will be enrolled in cohorts of 3 for each dose level. Dose escalation will proceed between each cohort and no intrapatient dose escalation will be allowed. If none of the first 3 subjects experiences a DLT, then dose escalation will proceed to the next cohort. If 1 of 3 subjects develops a DLT, the cohort will be expanded to 6 subjects. If no more than 1 subject of the 6 experience a DLT, then escalation to the next dose level will proceed. If 2 subjects in any dose level experience DLT, the dose escalation will be stopped and the prior dose level declared the MTD. A minimum of 6 evaluable subjects will be treated at the MTD dose level and no more than one of the 6 subjects may experience DLT at this dose level. The MTD will be considered as the recommended dose for future studies. At least 6 and up to 12 subjects with Ewing sarcoma (see inclusion criteria) will be entered at the MTD to more accurately estimate the incidence of systemic toxicities, characterize PK, and measure a preliminary estimate the tumor response rate. This study has accrued 25 patients in the dose escalation phase and is expected to accrue up to 12 patients total per histology including the expansion cohort (Ewing sarcoma, osteosarcoma, neuroblastoma and rhabdomyosarcoma which demonstrated an objective response in the dose escalation phase)for a total of up to 75 patients.

12.2 General Considerations

This study is a phase I trial whose primary objective will be to determine the maximum tolerated dose (MTD) and safety of MM-398 in combination with intravenous cyclophosphamide in patients with recurrent or refractory pediatric solid tumors. The study will be conducted within the SPOC Consortium. The SPOC Operations Center at Texas Tech University Health Sciences Center School of Medicine Cancer Center (TTUHSC) will be the coordinating center for this study and will be responsible for patient registration and maintaining a database of study information. Toxicity will be graded according to the NCI Common Toxicity Criteria (CTC) version 4.0 (http://ctep.cancer.gov)

Decisions about dose escalation, de-escalation, and determination of MTD will be based on observations made after the first course of therapy.

Patients who do not receive at least 85% of the required dose of MM-398 for any reason other than toxicity or intolerability of the regimen, and who do not experience toxicity, will not be counted for purposes of dose escalation and will be replaced.

A standard 3+3 design dose escalation design to MTD will be used. The statistical analysis will be descriptive and the use of any inferential statistics will be exploratory. Safety data will be summarized for the safety population, comprising all enrolled subjects who have been administered any study medication. All available data and tabulation of results will be displayed by dose group.

1. Three patients are entered at the first dose level

2. If 0/3 experiences DLT at a given dose level, then the dose is escalated to the next higher level and three patients are enrolled.

3. If 1/3 experiences DLT at current dose, then up to three more patients are accrued at the same dose level.

4. If 2 or more DLTs are observed in a three-patient or six-patient cohort at a given dose level, then the MTD has been exceeded, dose escalation will be stopped, and up to three additional patients will be enrolled at the next lower dose level (unless six patients have already been treated at that prior dose).

Enrollment will stop when 6 patients have been treated at the highest possible dose level at which 1 or fewer patients experience a DLT.

Estimation of the pharmacokinetic parameters will be performed using Non-Linear Mixed Effects Modeling. Additional exploratory analysis may be performed on the PK samples, to help clarify any safety, efficacy or PK issues related to MM-398 that arise during the course of the study.

The MTD is the highest dose level tested at which 0/6 or 1/6 patients experience DLT with at least 2/3 or 2/6 patients encountering DLT at the next higher dose. In light of the robust preclinical studies with MM-398 in Ewing sarcoma (which include a molecular marker of response for SN38 in Ewing) an expansion cohort of 12 patients with Ewing sarcoma will be accrued at the MTD of the study to enable a more accurate determination of systemic toxicities, PK and a preliminary assessment of activity for MM-398 in Ewing. Should fewer than 6 Ewing sarcoma patients be entered onto the study at the MTD or the dose just prior to the MTD, than accrual of 12 Ewing sarcoma patients at the MTD will proceed, which is justified based on the preclinical and molecular marker of response data (in preclinical studies) for MM-398.

Tumor responses will be measured and recorded, approximately every 6 to 8 weeks by using the RECIST guidelines (version 1.1). The local radiologist and/or PI assessment will determine disease progression.

In addition, at the MTD, an expansion cohort of up to 12 patients will also be accrued for other histological types for which objective responses are observed that benefit or have the potential to benefit patients, if drug supplies are available for such additional expansion cohorts.

These expansion cohorts will insure that adequate numbers of patients are accrued at the MTD to define the pharmacokinetics of MM-398, the systemic toxicities at the MTD, and to obtain an estimation of activity for MM-398 + cyclophosphamide.

12.3 Patient Disposition

The outcome status (in terms of number of courses of MM-398 received, toxicity, response, reason off study, time to progression, and survival) of all registered patients will be reported.

12.4 Statistical and Analytical Plans

All data will be monitored by the SPOC Operations Office and the Study Chair. Dose-limiting toxicities will be reviewed by the study committee, as will toxicity data at the completion of a dose level prior to dose-escalation. In general reviews and discussion will be conducted by email, unless events dictate potential amendments to the study, at which time teleconferences will be scheduled.

The SPOC Data Monitoring and Safety Committee (DSMC) will be informed by email of all adverse events and at the completion of each dose escalation. Any event requiring an amendment of the protocol for toxicity or dose-reduction from planned dose escalations will be reviewed and approved by the DSMC before implementation. Similarly, if the relationship between UGT1A1 polymorphisms and systemic toxicity (see 8.2.4) warrants implementing assessing UGT1A1 in the context of dose-escalation, the data will be reviewed by the study committee and the DSMC before implementation.

When an apparent MTD is achieved the study committee will review all toxicity and activity data and will determine if proceeding to the expansion cohort(s) is warranted. Response data from the expansion cohort will be considered descriptive but will be used to inform potential future clinical trials. In general, if fewer than 2 objective responses are seen in any expansion cohort (at the MTD) then enthusiasm for MM-398 + cyclophosphamide in the cohort that was tested would be diminished.

Pharmacokinetic data will be analyzed using Non-Linear Mixed Effects Modeling by the study pharmacologist (Dr. Kang). Additional exploratory analysis may be performed on the PK samples, to help clarify any safety, efficacy or PK issues related to MM-398 that arise during the course of the study.

13.0 STUDY ADMINISTRATION

13.1 Pre-Study Documentation

Prior to enrollment written documentation of patient eligibility including pathology reports, laboratory results, in accordance with inclusion and exclusion criteria.

13.2 Source Documentation

All patient data must have supportive source documentation in the medical records, or equivalent, before they are transcribed onto the case report form (CRF). Source documents, including test results and/or assessments (eg, clinical laboratory test results and efficacy measurements) collected or performed by institutions outside of the study center, are retained by the study center.

13.3 Trial Ethics

Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

13.4 Patient Informed Consent

A signed and dated informed consent form will be obtained from each parent/guardian and a signed and dated assent form will be obtained from each patient over 7 years of age, or as required by local regulations or institutional policy, before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to local IRB/IEC requirements. The patient's willingness to participate in the study will be documented in this assent form, which will be signed by the patient with the date of that signature indicated. The investigator will keep the original consent/assent forms and copies will be given to the patients. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the patient will be given to all patients.

13.5 Investigational Review Board or Ethics Committee Approval

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given center before the IEC/IRB and health authority (where applicable) for the center give written approval or a favorable opinion.

13.6 Monitoring

To ensure compliance with GCP, the study monitor or representative is responsible for ensuring that the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines. SPOC will carry out "virtual monitoring" of this study, with on site visits as needed. SPOC will allow audits that the manufacturer, Ipsen Pharmaceuticals, wishes to undertake.

13.7 Confidentiality

Each investigator must assure that the privacy of the patients, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.8 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the patients or when the change involves only logistics or administration. Each principal investigator and the sponsor will sign the protocol amendment.

Protocol Deviations, Violations, and Exceptions

A protocol deviation is non-adherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study. A protocol violation is any significant divergence from the protocol, ie, non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study center personnel, on the CRF.

13.9 Publication

The IND sponsor is responsible for preparing a clinical study report for the FDA, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator. When SPOC generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator when required by local regulatory agencies.

All unpublished information given to the investigator by Ipsen Pharmaceuticals shall not be published or disclosed to a third party without the prior written consent of Ipsen Pharmaceuticals. The primary publication from this study will report the results of the study in accordance with the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” as established by the International Committee of Medical Journal Editors (1997).

One or more papers describing the results of this study will be submitted to peer-reviewed journals. Authorship will be restricted to parties who have editorial or conceptual input to protocol design, analysis, and manuscript preparation.

13.10 Record Retention

Investigator responsibilities: Source data for safety assessments will be retained by each investigator for at least 25 years after the approval of the marketing application or withdrawal of the product from development. All other source data, source documents, CRFs, copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, informed consent forms, and other essential documents must be retained for a period of at least 2 years after the last approval of a marketing application 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. SPOC will inform each investigator/institution when these documents need no longer be retained. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the sponsor.

Sponsor responsibilities: The sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the sponsor's SOPs for clinical studies. If data management and filing for this study are delegated to a contract organization, these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor prior to the start of data management and filing activities. The original CRFs will be archived by the sponsor for the lifetime of the product.

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15.0 Sample Informed Consent

INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

South Plains Oncology Consortium (SPOC)

Protocol: SPOC-2012-001

Phase 1 Dose-escalating Study of MM-398 (Irinotecan Sucrosofate Liposome Injection) plus Intravenous Cyclophosphamide in Recurrent or Refractory Pediatric Solid Tumors

When we use "you" and "I" in this consent form, we mean you or your child.

This study is a clinical trial (a research study involving patients, or protocol) of an experimental new drug for cancer. We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point. Clinical trials only include patients who choose to take part. Your participation in this study is entirely voluntary. Please read the consent form carefully. You will be given a copy of it to keep if you decide to participate in this study. You may discuss your decision with your friends and family if you would like.

This study is being carried out by the South Plains Oncology Consortium (SPOC). SPOC is an research group that consists of six hospitals that treat children with cancer in Texas and Oklahoma. It is common medical practice to treat children with cancer on research studies like this one.

This is a phase I study of the combination of two drugs: MM-398 and cyclophosphamide. This is called a Phase I study because the goal is to find the highest dose of MM-398 that we can give safely when it is used together with the chemotherapy drug M cyclophosphamide. We are using MM-398 because it seems to work against cancer in test tubes and animals. It may be most effective when it is given with standard chemotherapy. The combination of these two agents together has never been administered to children. MM-398 contains irinotecan in a specialized delivery system. Irinotecan is approved and used for the treatment of other types of cancer. This drug is considered experimental because its specialized formulation has not been tested in children. Similarly, cyclophosphamide is approved and used for the treatment of other types of cancer drug. The combination of these two drugs together is experimental. We do not know if this combination of medicines will work in people. There is a lot that we do not yet know about this combination of medicines.

You are being asked to participate in this study because you have a recurrent or progressive tumor that cannot be cured by any known standard treatment.

Why is this study being done?

We are testing new experimental drug combinations such as the combination of MM-398 and cyclophosphamide in the hopes of finding a drug that may be effective against tumors that have come back or that have not responded to standard therapy.

The goals of this study are:

- **To find the highest safe dose of MM-398 that can be given together with cyclophosphamide without causing severe side effects;**

- **To learn what kind of side effects this two drug combination can cause;**
- **To learn about the effects of MM-398 and the combination of MM-398 and cyclophosphamide on specific molecules in tumor cells;**
- **To determine whether the combination of MM-398 and cyclophosphamide is a beneficial treatment for your tumor.**

How many people will take part in the study?

There will be up to 75 patients participating in this study overall. About 7 will be treated at this hospital.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A medical history
- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests (including UGT1A1 *1 and *28 allele testing and possible research testing depending on UGT1A1 result)
- Urine tests
- Pregnancy test (if you are a female who could have children)
- Studies to evaluate disease (MRI, CT, bone marrow etc)

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, Cyclophosphamide will be given intravenously for the first five days of treatment and MM-398 will be given as an intravenous infusion on the third day of treatment. This pattern will be repeated every three weeks. This three week period is called a course. You may continue to receive this two drug combination for up to twelve months unless you develop serious side effects or your tumor worsens.

During this study, you will continue the antibiotic your doctor prescribes to prevent pneumonia (pneumocystis pneumonia or PCP). In addition, during this study your doctor may prescribe an antibiotic to help prevent diarrhea. This antibiotic should be started 2 days before you receive the first doses of MM-398 and cyclophosphamide. The antibiotic should be given throughout treatment on this study.

Cyclophosphamide will be given as an intravenous (IV) infusion over 30 minutes on days 1-5 of treatment. MM-398 will be given as an intravenous (IV) infusion over 90 minutes on the third day of treatment. The treatment is summarized in this table:

Week	**Week 1**					**Weeks 2-3***
Day (21 day cycle)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Days 6 - 21**
Cyclophosphamide, given by IV	**CPM**	**CPM**	**CPM**	**CPM**	**CPM**	**No chemotherapy** **Rest and evaluations**
MM-398 given by IV			**MM-398**			

MM-398 and cyclophosphamide are given directly into the vein through either a needle or small tubing

inserted each treatment day or through a long-term catheter called a central line*.

*Your physician may recommend that you have a central venous line placed. A central line is a special type of tubing inserted into a large vein in the chest by a surgeon during a short operation. Children are anesthetized for this procedure and receive pain medication afterwards to keep them comfortable. The central line is used to administer chemotherapy drugs and to withdraw small amounts of blood for testing during treatment. The risks associated with central lines will be explained to you and all of your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign.

The dose for the first children enrolled on the study was based on side effects seen when the medicines have been given separately. Between 2 and 6 children received the combination of MM-398 and cyclophosphamide at each dose. Patients enrolled early in this study received a lower dose of MM-398 than those who are enrolled later. As a patient enrolled in this study at a high dose level, it is possible that you will receive a dose that is more likely to cause side effects. Dosing is done this way because we do not yet know the best doses and schedules of the two drugs in combination to use in children. The doses used in the study going forward were determined by the previous patients' side effects and tolerability of the study drug combination.

You will also be given the following tests and procedures during the study. They are part of regular cancer care.

- Physical exam
- Blood tests
- Urine tests
- Pregnancy test
- Tests of heart function (ECHO, ECG)
- Studies to evaluate disease (MRI, CT, Bone marrow etc)

These tests are all necessary to make sure that you are not having unsafe side effects and to see whether or not your tumor is responding to the combination of MM-398 and cyclophosphamide.

Copies of the scans used to check the extent of your disease will be sent to central review centers as part of SPOC quality control. We would also like to do some extra tests called pharmacokinetic studies. These tests will help us learn how children clear MM-398 from their bodies and this information may help children who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be returned to you.

How long will I be in the study?

You may be in the study for up to 12 months if you are responding to therapy. Your doctor may decide to take you off study if any of the following occur:

- The side effects of the combination of MM-398 and cyclophosphamide are too harmful for you
- You need a treatment that is not allowed on this study
- Your tumor does not improve or worsens
- You are not able to follow study-related treatment instructions
- New information becomes available
- The study is not in your best interest
- The study is stopped

After you are finished taking this combination of medicines the study doctors will ask you to visit the office for follow-up exams as they would normally do for patients with solid tumors.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the combination of MM-398 and cyclophosphamide can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. For example, your health care team may prescribe medications to help prevent or control diarrhea if it develops during the study. Many side effects go away soon after you stop taking the combination of MM-398 and cyclophosphamide. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Because MM-398 is a new formulation of irinotecan many of the possible risks and side effects of MM-398 may be similar to that seen with irinotecan. We hope that this formulation will have less side effects irinotecan but we will not know for certain until completion of the study. Risks and side effects related to irinotecan include those which are:

Likely	Less Likely	Rare but serious

• Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light.
• Nausea
• Vomiting
• Loss of appetite
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells can make it easier to get infections
• Fever
• A feeling of weakness and tiredness
• Hair loss
• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
• An increase in the blood of a type of white blood cell
	• Fewer red blood cells and platelets in the blood.
	  ○ A low number of red blood cells can make you feel tired and weak
	  ○ A low number of platelets causes you to bruise and bleed more easily
	• Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which could cause excessive loss of water and salts from the body
	• Constipation
	• Pain at the injection site
	• A slow heart beat
	• Low blood pressure
	• Shortness of breath with cough
	• Rash
	• Headache
	• Acid or an upset stomach (heartburn)
	• Confusion or sleepiness
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening
		• Inflammation of the lungs which could lead to chest pain and shortness of breath and which may be life-threatening
		• Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain
		• Blood clots which may be in rare cases life-

called an eosinophil. These are sometimes associated with allergic reactions. • Inflammation and/or sores in the mouth, throat and/or esophagus • Infections		threatening • A stoppage (or blockage) of the intestine which may require treatment

MM-398 and Irinotecan can cause bad diarrhea or other digestive problems. Not all subjects will have bad diarrhea or other digestive problems. Using the supportive care drug loperamide (also known as Imodium) may help prevent diarrhea. Using an antibiotic (Cefixime or available equivalent) might also help prevent diarrhea when irinotecan is given. However, there is some risk that using an antibiotic to prevent diarrhea when subjects are getting irinotecan may cause inflammation of part of the large bowel. It may also cause bacterial infections in the blood. This is because the blood counts are low after chemotherapy drugs are given. If you get antibiotics and still have bad diarrhea or low white blood cell counts, we will lower the dose of irinotecan you get.

Risks and side effects related to cyclophosphamide include:

Likely	Less Likely	Rare but serious
• Loss of appetite • Nausea • Vomiting • Fewer white blood cells in the blood. ○ A low number of white blood cells may make it easier to get infections. • Hair loss • Decreased ability of the body to fight infection • Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children	• Abnormal hormone function which may lower the level of salt in the blood • Abdominal pain • Diarrhea • Fewer red blood cells and platelets in the blood ○ A low number of red blood cells may make you feel tired and weak. ○ A low number of platelets may cause you to bruise and bleed more easily. • Bleeding and inflammation of the urinary bladder • Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children • Temporary blurred vision • Nasal stuffiness with IV infusions • Skin rash • Darkening of areas of the skin and finger nails • Slow healing of wounds • Infections	• Heart muscle damage which may occur with very high doses and which may be fatal • Abnormal heart rhythms • Damage and scarring of lung tissue which may make you short of breath • A new cancer or leukemia resulting from this treatment. • Damage or scarring of urinary bladder tissue • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • Infertility which is the inability to have children

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Risks and side effects related to cefixime (an antibiotic which may be used to prevent or control diarrhea) include those which are:

Less likely:

- Diarrhea
- Stomach pain
- Nausea
- Vomiting
- Indigestion

Rare but can be serious:

- Headache
- Dizziness
- Seizures
- Life-threatening allergic reaction
- Over-reaction of the immune system to a medicine or drug
- Decrease in the number of red and white blood cells and platelets made in the bone marrow
- Inflammation of the intestines which can cause changes to bowel movements
- Changes to laboratory tests that could indicate liver damage
- Inflammation of the liver
- Yellowing of the skin
- Redness and blistering on the mouth, eyes and genitals, causing you to feel unwell with a high temperature, and causing difficulty eating and drinking; may require admission to the hospital

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study might affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

Risks of blood drawing or placing an intravenous catheter for blood drawing:
Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

<u>Bone Marrow Examination Risks:</u>
The test may be painful. There is also a small risk of infection or bleeding. The pain normally lessens within minutes to hours.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

The potential benefit of the treatment with the combination of MM-398 and cyclophosphamide is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. Because there is not much information about the effect this combination on cancers in humans, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**

- **No further treatment, and comfort care only**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The South Plains Oncology Consortium**
- **Representatives of the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **Pharmaceutical Collaborator (the company that makes MM-398)**

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The pharmaceutical company which makes MM-398 will provide the MM-398 at no charge while you take part in the study. The pharmaceutical company does not cover the cost of getting the cyclophosphamide ready and giving it to you, so you or your insurance company may have to pay for this. Costs associated with cyclophosphamide must be covered by you or your insurance company.

Even though it probably won't happen, it is possible that the pharmaceutical company MM-398 may not be able to continue to provide the MM-398 for some reason. If this would happen, the study may have to close. Your study doctor will talk with you about this, if it happens

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at **http://cancer.gov/clinicaltrials/learning/insurance-coverage/**. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____*[name of center]*Institutional Review Board (a group of people who review the research to protect your rights) at _____*(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org.

If you are in the United States, you may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. You will be given a copy of the protocol (full study plan) upon request. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all 13 pages of this form (including the study chart).
I have read it or it has been read to me.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant _____

Signature of Participant / Parent (or Guardian) _____ Date_____

Signature of Participant / Parent (or Guardian) _____ Date_____

Signature of Physician or Responsible Investigator _____ Date_____

APPENDIX I: Clinical Investigations and Tests

STUDY CHART

You will receive MM-398 and cyclophosphamide every 3 weeks in this study. This 3 week period of time is called a cycle. Each cycle is numbered in order. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Cycles 1 and 2*

Day	What you do
Before beginning the study	• Routine blood tests and assessment of the tumor
Cycle 1, Day 1	• Receive IV cyclophosphamide
Cycle 1, Day 2	• Receive IV cyclophosphamide
Cycle 1, Day 3	• Receive IV cyclophosphamide and IV MM-398
Cycle 1, Day 4	• Receive IV cyclophosphamide
Cycle 1, Day 5	• Receive IV cyclophosphamide
Cycle 1, Day 8	• Routine blood tests
Cycle 1, Day 15	• Routine blood tests
Cycle 1, Day 22	• Start cycle 2 if treatment parameters met (this is the same day as Cycle 2, Day 1)
Cycle 2, Day 1	• Get routine blood tests and receive IV cyclophosphamide.
Cycle 2, Day 2	• Receive IV cyclophosphamide
Cycle 2, Day 3	• Receive IV cyclophosphamide and IV MM-398
Cycle 2, Day 4	• Receive IV cyclophosphamide
Cycle 2, Day 5	• Receive IV cyclophosphamide
Cycle 2, Day 8	• Routine blood tests
Cycle 2, Day 15	• Routine blood tests
End of cycle 2	• Routine blood tests and assessment response of the tumor
Cycle 2, Day 22	• Start cycle 3 if treatment parameters met (this is the same day as Cycle 3, Day 1)
Cycle 3, Day 1*	• For patients whose disease is stable or improving, therapy may continue and will be repeated every three weeks as shown in cycle 2. • Tumor evaluation will occur after cycles 2, 4, 7, 10 (and every 3rd cycle thereafter)

*And all other cycles

APPENDIX II: Performance Status Scales/Scores

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		**Karnofsky**		**Lansky***	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III: Proposed Algorithm for Diarrhea Management

Supportive Care: Management of Diarrhea associated with MM-398

For patients with onset of diarrhea during or several hours after the infusion of MM-398, consider treating with atropine (suggested dose 0.01 mg/kg IV, maximum dose 0.4 mg).

For patients with diarrhea beginning eight hours or later following MM-398, Loperamide may be given. Dosing recommendations are based on weight

Under 13 kg:

- Take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 3 hours.
- During the night, the patient may take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 4 hours.
- Do not exceed 4 mg per day.

From 13 kg to less than 20 kg:

- Take 1 mg (1 teaspoonful of the 1 mg/5 mL oral solution or one-half capsule or tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution) every 3 hours.
- During the night, the patient may take 1.0 mg (one teaspoonful of the 1 mg/5 mL oral solution) every 4 hours.
- Do not exceed 6 mg per day.

From 20 kg to less than 30 kg:

- Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half capsule or tablet) every 3 hours.
- During the night, the patient may take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 caplet) every 4 hours.
- Do not exceed 8 mg per day.Do not exceed 8 mg per day.

From 30 kg to less than 43 kg:

- Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half capsule or tablet) every 2 hours.
- During the night, the patient may take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 4 hours.
- Do not exceed 12 mg per day.

>43kg and adults:

- Take 4 mg (4 teaspoonfuls of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (2 teaspoonfuls of the 1mg/5 mL oral solution or 1 capsule or tablet) every 2 hours.
- During the night, the patient may take 4 mg (4 teaspoonfuls of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours.

- Do not exceed 16 mg per day.

Failure of loperamide to control diarrhea within 24 hours of onset:

- Begin octreotide (Sandostatin®), 1-2 mcg/kg/dose SQ or IV every 12 hours.
- Dose may be titrated up to 10 mcg/kg/dose (maximum dose: 500 mcg) every 8 hours.

Antibiotics for GI Toxicities: cefpodoxime (Vantin®) and cefixime (Suprax®) should be considered for patients who develop Grade 3 or 4 gastrointestinal (GI) toxicity following MM-398 therapy. Toxicities include:

1) **Abdominal Pain:** Severe pain, pain or analgesics severely interfering with activities of daily living, disabling.

2) **Colitis (Grade 3 or 4):** Abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation of perforation or requiring surgery or toxic megacolon

3) **Dehydration:** Requiring IV fluid replacement (sustained), physiologic consequences requiring intensive care, hemodynamic collapse.

4) **Diarrhea:** Increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration, severe increase in loose stool, physiologic consequences requiring intensive care, hemodynamic collapse, or watery stool output compared with pretreatment, interfering with normal activity, physiologic consequences requiring intensive care, hemodynamic collapse.

5) **Vomiting:** ≥ 6 episodes in 24 hours over pretreatment, or need for IV fluids requiring parenteral nutrition, or physiologic consequences requiring intensive care, hemodynamic collapse.

6) **Weight Loss** ≥20% of body weight

Antibiotic Dosing:

- **Cefpodoxime:** 10 mg/kg/day, divided in 2 oral doses; maximum daily dose 400 mg for children < 12 years and maximum daily dose 800 mg for those ≥ 12 years), **OR**
- **Cefixime:** (8 mg/kg/dose as a single daily oral dose or divided BID; maximum daily dose 400 mg).

The antibiotic should be started 5 days prior to the start of MM-398 therapy only if the patient experienced Grade 3 or 4 colitis, dehydration, diarrhea, abdominal pain, weight loss or vomiting during prior therapy with MM-398. If it is not feasible to start cefpodoxime or cefixime 5 days prior to therapy with MM-398, give at least 1 full day of cefpodoxime or cefixime prior to the start of MM-398 course. Refer to institutional guidelines for administration. Adapted from Perry MC ed, et al: Companion Handbook to Chemotherapy Source Book. 2nd ed. Baltimore, MD:Lippinkott, Williams and Wilkins, 2004 and the COG Supportive Care Guidelines at https://members.childrensoncologygroup.org/_files/protocol/Standard/SupportiveCareGuidelines.pdf.