MM-398-01-01-02: A Phase 1 Study in Patients Treated with MM-398 (Nanoliposomal Irinotecan, nal-IRI,) to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages and to Predict Patient Response to Treatment

IPSEN Bioscience, Inc.

Version 6.0: **03Apr2017**
IND #: **102799**
EUDRA CT #: **2014-003673-42**
ClinicalTrials.gov ID: **NCT01770353**

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
ASCO	American Society of Clinical Oncology
BC	Breast cancer
BUN	Blood urea nitrogen
CES	Carboxylesterase
CL	Clearance
Cmax	Maximum concentration
CNS	Central nervous system
CRC	Colorectal cancer
CSF	Colony-stimulating factor
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EPR	Enhanced permeability and retention
ER	Estrogen Receptor
FACS	Fluorescence activated cell sorter
FMX-MRI	Ferumoxytol magnetic resonance imaging
FMX	Ferumoxytol
5-FU	5-Fluorouracil
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GGT	Gamma-glutamyl transferase
GSF	Growth stimulating factor
G-CSF	Granulocyte colony-stimulating factors
HPLC	High pressure liquid chromatography
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liter
LV	Leucovorin
mg	Milligram
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
ng	Nanogram

nm	Nanometer
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamic; or Progressive disease
PET	Positron emission tomography
PK	Pharmacokinetic
PI	Principal investigator
PR	Progesterone Receptor
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
$t_{1/2}$	Half-life
TOP-1	Topoisomerase-1
TAM	Tumor associated macrophages
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
Vss	Volume at steady state
WBC	White blood count

1 Synopsis

Sponsor	IPSEN BIOSCIENCE, Inc 650 East Kendall Street, Cambridge MA 02142 - USA
Protocol Title	A Phase 1 Study in Patients Treated with MM-398 (Nanoliposomal Irinotecan, nal-IRI,) to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages and to Predict Patient Response to Treatment
Protocol Number	MM-398-01-01-02
Phase of Development	Phase 1
Trial Locations	USA
Number of sites	Multiple sites
Primary Objectives	**Pilot Phase (Completed):** In patients with non-small cell lung cancer (NSCLC), colorectal cancer (CRC), triple negative breast cancer (TNBC), ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, gastroesophageal junction (GEJ) adenocarcinoma or head and neck cancer, who are undergoing therapy with MM-398: • To evaluate the feasibility of delayed ferumoxytol MRI (FMX-MRI) to identify tumor associated macrophages (TAM) • To measure tumor levels of irinotecan and SN-38 **Expansion Phase:** In patients with locally advanced or metastatic breast cancer: • To further investigate the feasibility of ferumoxytol (FMX) quantitation in tumor lesions • To characterize the relationship between ferumoxytol (FMX) tumor uptake and tumor response to MM-398
Secondary Objectives	**All Phases:** • To characterize the safety profile of MM-398 in the presence of FMX • To assess tumor response to treatment • To characterize the pharmacokinetics (PK) of MM-398 **Pilot Phase (Completed):** • To estimate the correlations between FMX-MRI, TAM levels, and tumor levels of irinotecan and SN-38 with administration of MM-398 • To determine the value of FMX-MRI in directing tissue biopsy **Expansion Phase:** • To characterize the efficacy of MM-398 in patients with locally advanced or metastatic breast cancer using key efficacy indicators such as objective response rate and clinical benefit rate • To further characterize the safety profile of MM-398, in the presence of FMX, in patients with locally advanced or metastatic breast cancer • To assess the association between deposition, as visualized by ferumoxytol imaging, and measures of efficacy • To assess the analytical performance of FMX-MRI measurements and optimize FMX-MRI parameterization

Exploratory Objectives	**Pilot Phase (Completed):** • To estimate the correlations between potential pharmacodynamic markers (FMX-MRI, TAM, tumor irinotecan, tumor SN-38 levels) and safety • To estimate the correlations between potential pharmacodynamic markers (FMX-MRI, TAM, tumor irinotecan, tumor SN-38 levels) and tumor response • To characterize each tumor biopsy to permit multivariate comparative analyses between tumor characteristics, FMX-MRI signal and drug metabolite levels **Expansion Phase:** • To evaluate a set of potential biomarkers from tumor tissue and blood samples for their ability to predict PK and/or response to MM-398 treatment
Study Design	The Pilot Phase will enroll approximately 12 patients, up to 20 in total. The first three patients enrolled can have any solid tumor type; however subsequent patients must have NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, gastroesophageal junction adenocarcinoma or head and neck cancer. No more than three patients with ER/PR positive breast cancer can be enrolled in the Pilot Phase and similar restrictions may be placed on other tumor types to ensure a heterogeneous population. An Expansion Phase will enroll cohorts of single indications of patients with locally advanced or metastatic breast cancer in 3 cohorts of 10 patients each depending on sub-type of breast cancer: Cohort 1: ER and/or PR-positive breast cancer Cohort 2: TNBC Cohort 3: breast cancer with active brain metastasis There are four stages to this study: • Screening Period (-28 d): patients undergo screening assessments to determine if they are eligible for the study • Ferumoxytol Period (Day 1 – Day 2): patients receive ferumoxytol (FMX) infusion and undergo required FMX-MRI scans and prior to receiving MM-398 • MM-398 Treatment Period (C1D1 – progression of disease): patients receive an MM-398 starting dose of 60 mg/m^2 every 2 weeks which should be dose escalated to 80 mg/m^2 every 2 weeks in subsequent doses depending on patient tolerance , other required assessments, and a post-treatment biopsy 72 hours after first dose of MM-398 • Follow Up Period (+30 d from last dose): patients return to clinic 30 days following the last dose of MM-398 for final safety assessments MM-398 will be administered at a dose of 60 mg/m^2 every two weeks and patients will be treated until disease progression or unacceptable toxicity. The dose of MM-398 should be escalated to 80 mg/m^2 every two weeks depending on patient tolerance.

Estimated Number of Patients	Between 12 and 20 patients will be enrolled in the Pilot Phase of this study. The Expansion phase will enroll up to 30 evaluable patients, in three cohorts of approximately 10 patients. The total enrollment for the study will be approximately 45 patients.
Inclusion Criteria	All Phases a) Pathologically confirmed solid tumors that have recurred or progressed following standard therapy, or that have not responded to standard therapy, or for which there is no standard therapy, or who are not candidates for standard therapy. Pathologically confirmed solid tumors that have recurred or progressed following standard therapy, or that have not responded to standard therapy, or for which there is no standard therapy, or who are not candidates for standard therapy. 1. Pilot Phase: the first three patients enrolled may have any solid tumor type, however patients subsequently enrolled into the Pilot phase must have one of the following tumor types: NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma or head and neck cancer. 2. Expansion Phase: the following invasive breast cancer tumor sub-types are required: i. Cohorts 1 and 2 must be documented to be HER2 negative as outlined in the ASCO/CAP 2013 guidelines for HER2 testing, defined by at least one of the following: ▪ HER2 immunohistochemistry (IHC) staining of 0 or 1+, **OR** if HER2 IHC 2+ ▪ Negative by In-Situ Hybridization (ISH) based on defined as a Single-probe average HER2 copy number <4.0 signals/cell ▪ OR Negative by Dual-probe ISH defined as a HER2/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell ii. In addition, breast cancer patients must be able to be categorized into one of the following cohorts: ▪ **Cohort 1**: hormone receptor positive breast cancer patients with ER-positive and/or PR-positive tumors defined as ≥1% of tumor nuclei that are immunoreactive for ER and/or PR and HER2 negative ▪ **Cohort 2**: triple negative breast cancer (TNBC) patients with ER-negative, PR-negative tumors defined as < 1% of tumor nuclei that are immunoreactive for ER and PR and HER2 negative ▪ **Cohort 3**: Any sub-type of metastatic breast cancer and active brain metastases (see additional criteria o-r below)

	b) Documented locally advanced or metastatic disease with at least two radiologically measurable lesions as defined by RECIST v1.1 (except Expansion Phase Cohort 3, see inclusion criterion o below) c) ECOG performance status 0 or 1 d) Bone marrow reserves as evidenced by: • ANC > 1,500 cells/µl without the use of hematopoietic growth factors • Platelet count > 100,000 cells/µl • Hemoglobin > 9 g/dL e) Adequate hepatic function as evidenced by: • Normal serum total bilirubin • AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present) f) Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN g) Normal ECG or ECG without any clinically significant findings h) Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy i) At least 18 years of age j) Able to understand and sign an informed consent (or have a legal representative who is able to do so) <u>Expansion Phase additional inclusion criteria</u>: k) Received at least one cytotoxic therapy in the locally advanced or metastatic setting, with exception of TNBC patients who progressed within 12 months of adjuvant therapy l) Received ≤ 5 prior lines of chemotherapy in the metastatic setting (no limit to prior lines of hormonal therapy in Cohort 1) m) Candidate for chemotherapy n) At least one lesion amenable to multiple pass core biopsy (exception: Cohort 3 patients) <u>Expansion Phase **Cohort 3** additional inclusion criteria</u>: o) Radiographic evidence of new or progressive brain metastases after prior radiation therapy with at least one brain metastasis measuring ≥ 1 cm in longest diameter on gadolinium-enhanced MRI (note: progressive brain lesions are not required to meet RECIST criteria in order to be eligible; extra-cranial metastatic disease is also allowed) p) Imaging following prior radiation is not consistent with pseudo-progression in the judgment of treating clinician q) Neurologically stable as defined by: • Stable or decreasing dose of steroids and anti-convulsants for at least 7 days prior to study entry

	• No clinically significant mass effect, hemorrhage, midline shift, or impending herniation on baseline brain imaging • No significant focal neurologic signs and/or symptoms which would necessitate radiation therapy or surgical decompression in the judgment of the treating clinician r) No evidence of diffuse leptomeningeal disease on brain MRI or by previously documented cerebrospinal fluid (CSF) cytology. **NOTE**: discrete dural metastases are permitted.
Exclusion Criteria	1. Active central nervous system metastases, indicated by clinical symptoms, cerebral edema, or steroid requirement (applies to Pilot Phase and Expansion Phase Cohorts 1-2 only) 2. Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1 3. Have received irinotecan or bevacizumab (or other anti-VEGF therapy) within the last six months; and for Expansion Phase patients, have received any prior treatment with a Topo1 inhibitor (irinotecan-derived or topotecan) 4. History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years. 5. Unable to undergo MRI due to presence of errant metal, cardiac pacemakers, pain pumps or other MRI incompatible devices. 6. A history of allergic reactions to compounds similar to ferumoxytol as described in full prescribing information for ferumoxytol injection, or to other IV iron replacement products (e.g. parenteral iron, dextran, iron-dextran, or parenteral iron polysaccharide preparations); 7. Documented history of multiple drug allergies 8. Known hypersensitivity to any of the components of MM-398, or other liposomal products 9. Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease. • Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion • NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure 10. 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

	11. Prior chemotherapy administered within 3 weeks, or within a time interval less than at least 5 half-lives of the agent, whichever is longer, prior to the first scheduled day of dosing in this study 12. Received radiation therapy in the last 14 days 13. Evidence of Iron overload as determined by: • Fasting transferrin saturation of >45 % and/or • Serum ferritin levels >1000 ng /ml 14. Treated with parenteral iron in the previous 4 weeks 15. HIV-positive patients on combination antiretroviral therapy or other conditions requiring treatment where there is a potential for ferumoxytol to have negative pharmacokinetic interactions 16. 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 17. 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	Patients will be treated until disease progression, intolerable toxicity, or at the discretion of the treating physician. A follow up clinic visit is required 30 days after last dose to complete the final safety assessments.
Study Treatments	A single dose of 5 mg/kg of ferumoxytol will be administered at Day 1 as an IV infusion in 50-200 mL of 0.9% sodium chloride or 5% dextrose over a minimum period of 15 minutes following dilution. The total single dose will not exceed 510 mg, the maximum approved single dose of ferumoxytol. MM-398 monotherapy will be administered by intravenous (IV) infusion over 90 minutes at a dose of 60 mg/m^2 every two weeks. The dose of MM-398 should be escalated to 80 mg/m^2 in subsequent doses depending on patient tolerance.
Investigational Products	MM-398 is irinotecan (also known as CPT-11) encapsulated in a nanoliposomal drug delivery system. It will be supplied in sterile, single-use vials containing 10 mL of MM-398 at a concentration of 5 mg/mL. MM-398 must be stored refrigerated at 2 to 8°C, with protection from light. Ferumoxytol is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease. Although not an approved indication, ferumoxytol has been used as an MR contrast agent in various indications and healthy volunteers and will be utilized as such in this study. Ferumoxytol (30 mg/mL) is available for intravenous infusion in single use vials. Each vial contains 510 mg of elemental iron in 17 mL. Ferumoxytol must be stored at controlled room temperature (20° to 25°C).
Statistical Analyses	Between 12 and 20 patients will be enrolled in the Pilot Phase of this study, and approximately 30 patients in three Expansion Phase cohorts.

	The safety population will include all patients receiving at least one dose of MM-398 or ferumoxytol. The efficacy evaluable population includes all patients receiving at least one dose of MM-398. The pharmacodynamic evaluable population includes all efficacy evaluable patients with the following: a) pre-treatment FMX-MRI scan(s) and b) radiological scans at 8 weeks. The pharmacokinetic population includes patients receiving at least one dose of MM-398 and blood samples adequately collected at the predefined points. No formal hypothesis testing will be performed in the pilot or expansion phases of this study. Descriptive statistics will be calculated to summarize categorical and continuous parameters. Time to event parameters will be presented graphically using Kaplan-Meier estimates. Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported in the most current version of MedDRA. Tabular summaries will be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, and deaths, TEAE-related to MM-398 or ferumoxytol and TEAE Grade 3/4. Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where possible. Tumor evaluation will be measured according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 for non-CNS disease, or according to modified RECIST criteria as defined in this protocol for CNS disease. Tumor evaluations will be characterized according to best overall response (BOR), duration of response (DOR), progression-free survival (PFS), and clinical benefit rate (CR, PR, or SD $\geq$ 24 weeks). Objective response rate (ORR) and BOR will be summarized using frequency and percentage. PFS will be described using Kaplan-Meier methods. FMX uptake will be summarized as a continuous parameter. Box and whisker plots will be displayed for FMX uptake. The relationship between FMX uptake and tumor response will be evaluated using various parameters and methods. Relationships may be explored as appropriate. Additionally, informal Fisher's exact test will be used to investigate dichotomous FMX cut-points as related to ORR. Other graphical procedures may be implemented to explore the relationship between FMX and efficacy response. Spearman pairwise correlations will be computed between the following measurements: • FeMRI levels • Tumor associated macrophage levels • Tumor irinotecan levels • Tumor SN-38 levels Graphical and regression methods will be used to explore potential relationships among correlated measurements. In addition, relationships between

	pharmacodynamics markers and efficacy response will be evaluated in an exploratory manner. PK parameters will be derived from the blood PK samples and will be analyzed using descriptive statistics, including the median, mean and 95% confidence intervals around parameter estimates by dose level. All PK parameters will include Cmax, Tmax, AUC (area under the concentration curve), clearance, volume of distribution at steady state (Vdss), and the terminal elimination half-life. Estimation of the pharmacokinetic parameters will be performed using standard non-compartmental methods.
Sample Size Justification	No formal hypothesis testing will be performed for this study. The Pilot Phase will enroll 12-20 patients in a variety of indications, while the Expansion Phase will enroll approximately 30 patients with metastatic breast cancer within 3 cohorts. Although no formal sample size calculation was performed for either study phase, the anticipated response rate in the HER2 negative Expansion Phase is estimated around 29% [36].

2 Background Information and Rationale

MM-398 is irinotecan encapsulated in a nanoliposomal delivery system. Nanoliposome delivery reduces systemic exposure and increases drug accumulation within a tumor. Tumor associated macrophages (TAMs) appear to play a key role in the deposition, retention and activation of MM-398 within the tumor microenvironment. Ferumoxytol is an approved therapy that is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease; however a growing number of cancer patients without iron deficiency are being administered ferumoxytol as an imaging agent to visualize macrophage content and vasculature [1], [2]. This pilot study will evaluate the feasibility of measuring TAMs by utilizing ferumoxytol MRI (FMX-MRI) as an imaging agent and will also measure corresponding MM-398 metabolite drug levels, and their correlation. If successful, future studies will correlate macrophage profiling using FMX-MRI as a potential predictive biomarker for patients treated with MM-398.

To maximize the information from this study, patients that are most likely to achieve the objectives of the study will be enrolled. Although the first three patients enrolled in the study can have any solid tumor, subsequent patients will be limited to a subset of indications. Selection of these indications is based on the expected higher levels of tumor-associated macrophages, the potential sensitivity to irinotecan based on clinical experience and/or the presence of the pro-drug converting carboxyl esterase enzymes (CES) and the amenability to imaging and biopsy collection. These indications include colorectal cancer (CRC), non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), estrogen receptor and/or progesterone receptor (ER/PR) positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, gastroesophageal junction (GEJ) adenocarcinoma and head and neck cancer. No more than three patients with ER/PR positive breast cancer can be enrolled in the Pilot Phase of the study and similar restrictions may be placed on other tumor types to ensure a heterogeneous population at study end.

Merrimack Pharmaceuticals' tumor microarray analysis of patient samples showed that both colorectal CRC and NSCLC have a significant subset with higher levels of the CD68 marker for tumor associated macrophages. This is in agreement with published findings reviewed by Heusinkveld and van der Burg (2011) [24]. This review also provides supportive information on the presence of tumor-associated macrophages in other indications, including ovarian, gastric and pancreatic cancers. Head and neck cancer has been shown to achieve high deposition of pegylated liposomes in an imaging study by Harrington et al. (2001) [25] and contains many immune cells, including phagocytic dendritic cells and macrophages (reviewed in [26, 27]). In-house profiling of human primary xenografts showed high CES enzyme activity (measured by tumors ability to convert irinotecan to SN-38) in CRC and NSCLC patient tumor samples. Analysis of the gene expression of CES1, CES2 and topoisomerase 1 (TOP1) demonstrated high expression of TOP1 and CES2 particularly in breast cancer, as well as the mammary ductal carcinoma subtype. These higher expression levels were also seen in TNBC samples.

The use of irinotecan is well established in CRC as a single agent or in combination with 5-FU/LV in the first and second line [3]. Irinotecan has demonstrated efficacy in advanced NSCLC in a phase 3 setting both as a monotherapy and when combined with cisplatin [4]. Similarly, Nogami et al (2012) reported that in a phase II study the combination of irinotecan and amrubicin was effective in patients with relapsed NSCLC [5]. Combinations of cetuximab with irinotecan have shown promising responses particularly in TNBC [6] and more recently also in

gastroesophageal cancer [28, 29, 30]. Topoisomerase I inhibitors such as topotecan and irinotecan also provide very effective and tolerable treatment options for recurrent ovarian cancer [31]. Further, irinotecan has demonstrated efficacy in metastatic breast cancer [32, 33], and although not specifically approved for this indication, irinotecan is commonly used to treat patients with anthracycline and taxane pre-treated metastatic breast cancer [34].

In order to characterize MM-398 efficacy in the Expansion Phase of the study, as well as to explore the potential correlation between ferumoxytol (FMX) tumor uptake and tumor response to MM-398, cohorts of patients with a single indication will be enrolled. The Expansion Phase of the study will focus on patients with metastatic breast cancer stratified into cohorts of ER/PR positive breast cancer, TNBC, and patients with active brain metastases. In addition to having high unmet medical need and sensitivity to irinotecan based on clinical experience, preclinical studies in breast cancer models have demonstrated activity of pro-drug converting CES enzymes (unpublished data) as well as efficacy of MM-398 [35].

2.1 MM-398

MM-398 (also known as PEP02) is irinotecan (also known as CPT-11) encapsulated in a nanoliposome drug delivery system.

The active ingredient of MM-398 injection is irinotecan. 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 irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug [7], [8], [9]. Irinotecan is a pro-drug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38 [10]. 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 irinotecan [11], [12]. 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. 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.

Similar to other nanoparticles, MM-398 is a relatively large molecule measuring approximately 100 nm, and as such is not expected to diffuse easily into tumors in the same way as smaller molecules. It is therefore critical to understand the tracking, uptake and processing of MM-398 in the tumor micro environment in order to deliver the optimal therapeutic dose to the tumor.

2.1.1 MM-398 Pre-clinical Experience

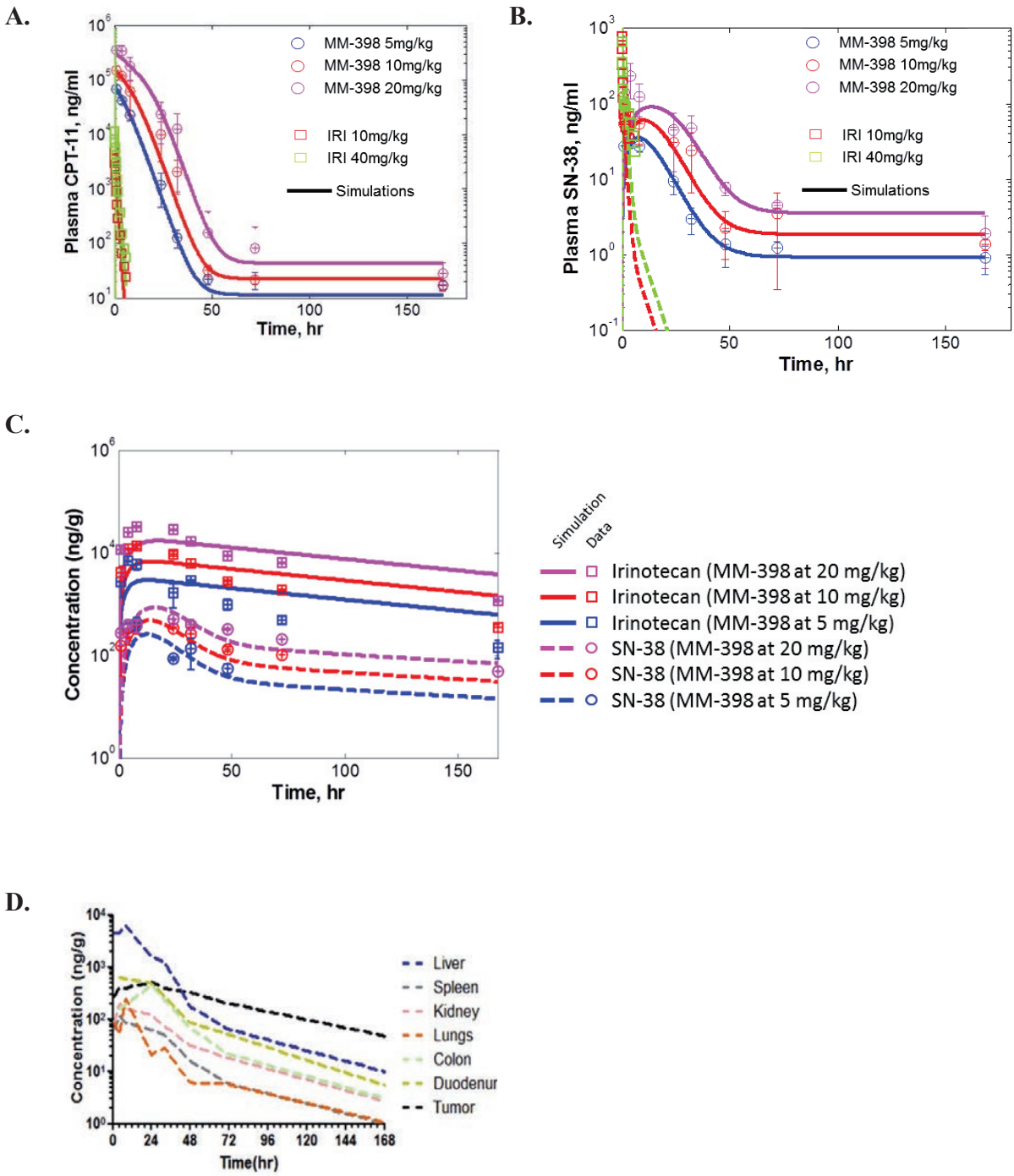
MM-398 has been shown in pre-clinical settings to have a broad spectrum of activity in a wide range of solid tumors including colon, pancreatic, gastric, cervical, non-small cell lung, small cell lung, ovarian, thyroid, and breast cancers, as well as glioma, Ewing's sarcoma, and neuroblastoma, often with a high degree of anti-tumor activity against resistant or difficult to treat cancer models. Nanoliposomal irinotecan, MM-398, 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 pancreatic model [13].

2.1.2 MM-398 Pre-clinical Pharmacokinetics

The pharmacokinetic (PK) properties of MM-398 were evaluated in an HT-29 colon subcutaneous xenograft model. Tumor bearing mice were injected with different doses of MM-398 (5, 10, 20 mg/kg) and following a single injection, plasma and tissue samples were collected at various time points (1, 4, 8, 24, 48, 72, 168 hours). HPLC analysis was used to measure the levels of the irinotecan and its metabolite SN-38 in these samples. The PK profile of MM-398 was compared with that of free irinotecan (at 10 and 40 mg/kg).

Both irinotecan and SN-38 are cleared very rapidly (within 8 hours) from the plasma following free irinotecan administration. However, MM-398 clearance is considerably slower with a half-life of approximately 48 hours as shown in Figure 1A; as >90% of irinotecan is encapsulated throughout in the plasma, irinotecan levels are reflective of MM-398 concentration. SN-38 plasma exposure is also greater though Cmax levels are reduced following MM-398 administration, suggesting the advantage of the irinotecan liposomal formulation in prolonging exposure and half-life (Figure 1B). Both irinotecan and SN-38 accumulate in tissues for extended time (at least 1 week after MM-398 administration). Also, the accumulation was observed to be dose-dependent (Figure 1C). When compared to accumulation in other organs, there were relatively higher levels of prolonged accumulation in the tumor compared to normal tissue where the metabolites are at very low levels after 48 hours (Figure 1D).

Figure 1: Summary of MM-398 PK Parameters in an HT-29 Xenograft Study



Plasma irinotecan (A) and SN-38 (B) levels following free irinotecan and MM-398 administrations. (C) Intratumor levels of irinotecan and SN-38 levels following a single MM-398 (20 mg/kg) dose. (D) Prolonged accumulation of SN-38 (~168 h) seen in tumor compared to other organs (~48 h).

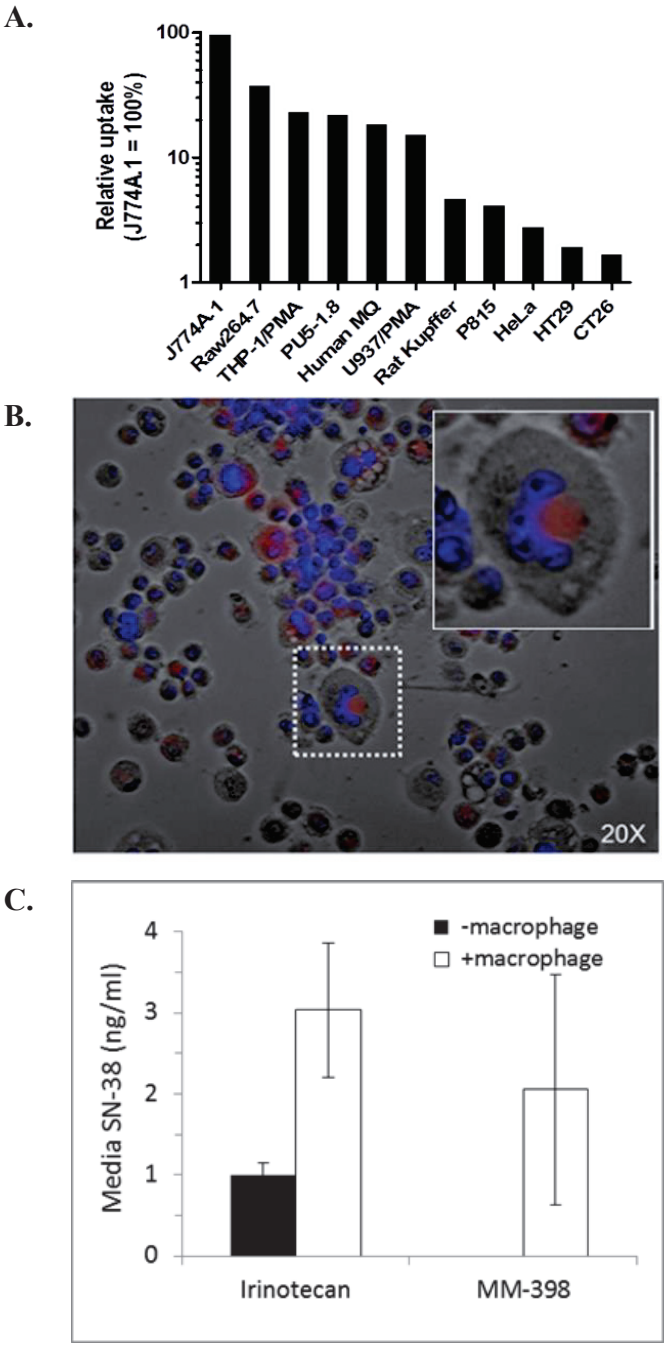
Activation of irinotecan to SN-38 by the liver is the primary path for SN-38 tumoral accumulation when free irinotecan is administered. In contrast, these data suggest that accumulation of MM-398 in the tumor and subsequent liposome breakdown and local conversion of irinotecan to SN-38 is responsible for the enhanced tumor exposure of SN-38 when MM-398 is administered. Current research is focused on identifying cell types located in the tumor responsible for liposomal breakdown and activation of MM-398.

2.1.3 Tumor Uptake and Local Tumor Activation of MM-398 by Macrophages

Tumor associated macrophages are a highly phagocytic cell type known to phagocytize liposomes. They express one of the carboxylesterase enzymes that are responsible for activation of the pro-drug irinotecan to the active SN-38 metabolite, making them a prime candidate for participating in the processing of MM-398 in the tumor [14].

Merrimack first determined whether macrophages take up liposomes using an in vitro cell based assay. Fluorescence activated cell sorter (FACS) analysis (Figure 2A) was performed to quantify the differential uptake of labeled (DiI5) liposomes (20 µg/ml, 24h) across multiple cell lines (macrophages and tumor cells). Relatively higher uptake was seen in phagocytic cell lines (J774.1, Raw264.7, THP-1, U937) compared to tumor cell lines (HT29, CT26, Hela). One of the macrophage cell lines, U937, was selected to test whether human macrophages can convert irinotecan to SN-38 when exposed to either free irinotecan or liposomal MM-398. This human monocytic cell line was differentiated into macrophages with phorbol-12-myristate-13-acetate to measure liposome uptake and drug conversion. Microscopy showed intracellular uptake of DiI5-labelled liposomes by macrophages (Figure 2B; blue: nucleus, red: liposomes). The cells were also incubated with either free irinotecan or MM-398 for 24 hours and the SN-38 released in the media was measured by high pressure liquid chromatography (HPLC) analysis (Figure 2C). A 2-fold increase in SN-38 levels released in the media was seen in the presence of macrophages as compared to the absence of macrophages. The data suggested high uptake of liposomes by macrophages and their ability to activate irinotecan.

Figure 2: **Macrophage Uptake by Liposomes and Tumor Activation**

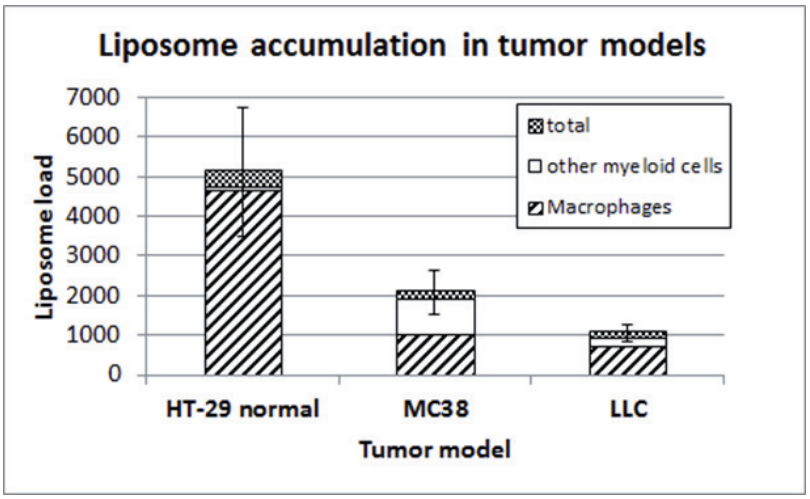


(A) FACS analysis comparing uptake of labeled (DiI5) liposomes by macrophages and tumor cells. (B). Human macrophage cell line U937 shows intracellular uptake of DiI5 label liposomes (red); nucleus (blue). (C) HPLC analysis to measure SN-38 levels in media when either irinotecan or MM-398 is incubated for 24 h in presence and absence of macrophages (U937 cells).

The ability of TAM's to phagocytize liposomes using ex-vivo FACS analysis was also measured. A number of tumor bearing mice models were injected with labeled (DiI5-liposomes) and tumors were collected 24 hour post injection. The tumors were digested, and FACS analysis was

performed to quantify the DiI5 signal in different cell populations (tumor cells, myeloid cells, macrophages). In all models macrophages captured the largest share of the overall liposomal accumulation in the tumor (Figure 3).

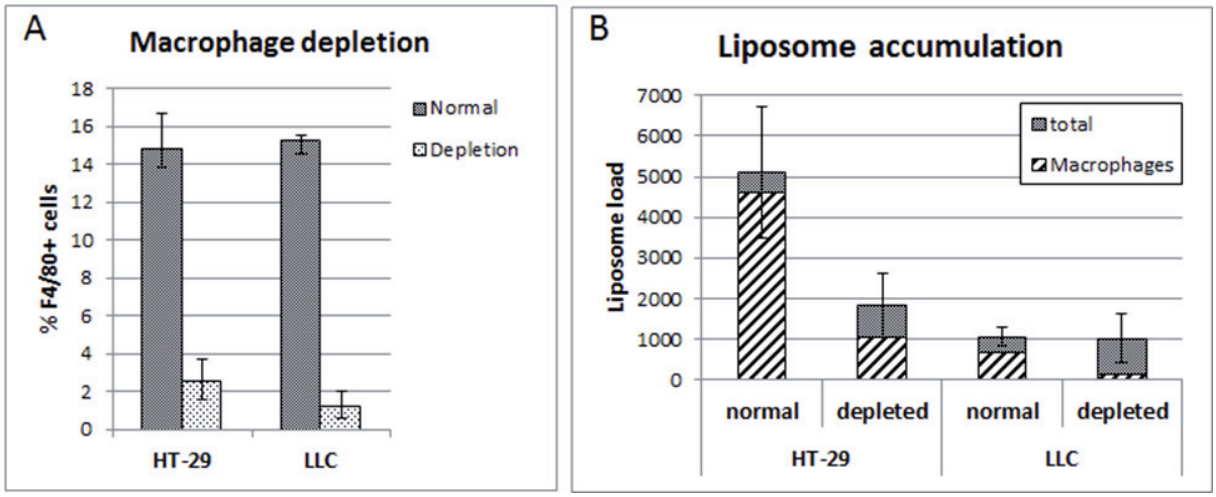
Figure 3: Liposome Accumulation in Tumor Models



Macrophages take up the largest share of liposomes in various tumor models as assessed by ex-vivo flow cytometry. Myeloid cells are CD45+CD11b+, while macrophages are also F4/80+ (N=4).

To confirm that MM-398 was predominantly phagocytized by TAM's compared to tumor cells, tumor bearing mice were pre-treated with anti-CSF-1 antibody to deplete TAM's, this antibody inhibits colony stimulating growth factor (CSF-1), which recruits macrophages [15]. Following TAM depletion, the mice were then injected with DiI5 labeled liposomes to measure the relative uptake of liposomes by various cell populations within the tumor. Ex-vivo FACS analysis confirmed the depletion of macrophages (Figure 4A), resulting in the expected robust decrease in the liposome accumulation associated with the macrophage cell population (Figure 4B).

Figure 4: Macrophage Depletion and Liposome Accumulation in a Tumor Bearing Mouse Model



(A) Ex-vivo FACS analysis of tumors from mice without and with depletion of macrophages showing depletion of tumor associated macrophages. (B) Reduction of liposomal accumulation in the depleted macrophage cell population. Depletion also reduces the overall liposomal load in the HT-29 tumors.

2.1.4 MM-398 Clinical Experience

Six clinical studies of MM-398 have been completed to date, with approximately 385 patients across multiple tumor types exposed to various dosing regimens (Table 1). Additionally, five studies are currently underway and actively recruiting patients across multiple tumor types (Table 2).

Table 1: Summary of Completed Studies with MM-398

Study	PEP0201	PEP0202	PEP0203	PEP0206	PEP0208	NAPOLI-1
Tumor Type	Solid tumors	Cervical	Solid Tumors	Gastric	Pancreas	Pancreas
Phase	1	1	1	2	2	3
Study design	Open label, dose escalation	Open label, dose escalation	Open label, dose escalation	Open label, 3 arm study comparing MM-398, docetaxel and irinotecan (44 patients/arm)	Open label, single arm	Randomized comparison of MM-398 and MM-398+ 5-FU/LV *vs* a common control of 5-FU/LV
Number of Patients treated with MM-398	11	6	16	44	40	151 (monotherapy) 117 (combination)
Dosing Frequency	Q3W	Q3W	Q3W	Q3W	Q3W	Q3W (monotherapy) Q2W (combination)
Dose Level (mg/m^2)	60 (n = 1) 120 (n = 6) 180 (n = 4)	60 (n = 3) 80 (n = 3)	60 (n = 3) 80 (n = 6) 100 (n = 5) 120 (n = 2)	120	120	120 (monotherapy) 80 (combination)
Combination	No	Cisplatin	5FU/LV	No	No	5FU/LV
Combination dose	---	60 mg	2000/500 mg/m^2	---	---	2400/400 mg/m^2
Key results	MTD identified as 120 mg/m^2	Study terminated due to protocol violation	MTD identified as 80 mg/m^2	Similar safety profile across irinotecan and MM-398 arms; 6 responses in MM-398 arm met primary endpoint (7.3 month mOS, 13.6% ORR)	Median survival of 5.2 months	Combination arm achieved median OS 6.1 months, 1.9 month improvement over control arm (HR=0.67; p-value=0.012) Q2W combination arm performed better than Q3W monotherapy (OS 6.1 vs 4.9 months)

Table 2: Summary of On-going Studies with MM-398

Study	UCSF 8603	PIST-CRC-01	PEPCOL	UCSF 13-12025		SPOC 2012-001	DOUBLIRI C13-4	MM-398-07-02-03
Tumor Type	Glioma	Colorectal	Colorectal	Glioma		Pediatric Solid Tumors	Colorectal	Pancreatic
Phase	1	1	2	1		1	1	2
Study Design	Open label, dose escalation	Open label, dose escalation	Comparison of MM-398 + 5FU/LV + avastin versus FOLFIRI + avastin	Open label, dose escalation using convection-enhanced delivery for direct tumoral injection		Open label, dose escalation	Open label, dose escalation. MM-398 + irinotecan	Comparison of MM-398 + 5FU/LV with or without oxaliplatin versus nab-Paclitaxel + gemcitabine
Dosing Frequency	Q3W	Q2W	Q2W	Single dose		Q3W	Q2W	Q2W
Dose Level (mg/m^2)	HTZ[a] 60 (n = 3) 90 (n = 5) WT[b] 120 (n = 6) 180 (n = 4) 240 (n = 3)	80 (n = 6) 90 (n = 6) 100 (n = 6)	80	Dose 20 mg 40 mg 60 mg 80 mg	Tumor Volume 1-4 cm^3 1-4 cm^3 2-5 cm^3 2-6 cm^3	60 (n = 1) 90 120 150 180 210	MM-398 60 (n = 3-6) 80 (n = 3-6)	80
Combination	No	No	5FU/LV	No		Cyclophosphamide	Irinotecan	5FU/LV ± Oxaliplatin
Combination Dose	---	---	2400/400 mg/m^2 (5FU/LV) 5 mg/kg (avastin)	---		250 mg/m^2	90 or 120 mg/m^2 (Irinotecan)	2400/400 mg/m^2 (5FU/LV) 60 or 85 mg/m^2 (oxaliplatin) 125/1000 mg/m^2 (nab-Pac/Gem)
Current Status	MTD identified for HTZ; escalation ongoing for WT	Enrollment completed in final cohort	Enrollment ongoing	Enrollment ongoing		Enrollment ongoing	Enrollment ongoing	Enrollment ongoing

[a] Heterozygous for UGT1A1*28
[b] Wildtype for UGT1A1*28

2.1.5 MM-398 Safety in Humans

The clinical safety profile of MM-398 is consistent with that seen with free irinotecan. Diarrhea is a frequent adverse event, while hematological toxicity is around 30%.

The overall safety profile of MM-398 is presented in detail in the related Investigator Brochure. In a 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 (Common Terminology Criteria for Adverse Events (CTCAE) version 3.0); neutropenia was the most common adverse event (30%), possibly related to prior therapy with gemcitabine. Abdominal pain, asthenia, anemia, hyponatremia, diarrhea and infection occurred in > 10% of patients. Table 3 provides a summary of the adverse events (AEs) observed in this study.

Table 3: Summary of Grade 3 or Higher Adverse Events in PEP208 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	8 (20%)	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	3 (7.5%)	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	1 (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%)

Additionally, the following safety data is available from a recently concluded Phase III study in pancreatic cancer (NAPOLI-1) comparing MM-398 + 5-Fluorouracil/Leucovorin (5-FU/LV), or MM-398 monotherapy, with 5-FU/LV alone (see Table 4).

Table 4: Summary of Grade 3 or Higher Adverse Events in NAPOLI Study

Grade ≥ 3 Non-hematologic AEs in > 5% Patients, %[a]	MM-398+5-FU/LV 80 mg/m^2 q2w (N=117)	MM-398 120 mg/m^2 q3w (N=147)	5-FU/LV (N=134)
Fatigue	14	6	4
Diarrhea	13	21	5
Vomiting	11	14	3
Nausea	8	5	3
Asthenia	8	7	7
Abdominal pain	7	8	6
Decreased appetite	4	9	2
Hypokalemia	3	12	2
Hypernatremia	3	6	2
Grade ≥3 Hematologic AEs Based on Laboratory Values, %[a,b]			
Neutrophil count decreased	20	16	2
Hemoglobin decreased	6	7	5
Platelet count decreased	2	1	0

[a] Per CTCAE Version 4
[b] Includes only patients who had at least one post-baseline assessment

2.1.5.1 Potential Toxicity of MM-398 in Humans

It has been shown in animal and human pharmacokinetics studies that once irinotecan is released from the MM-398 liposomes, the conversion of irinotecan to SN-38 is similar to that of the unencapsulated irinotecan. Because the active pharmaceutical ingredient in MM-398 is irinotecan, the safety profile is anticipated to be similar. In addition to the adverse events noted in Table 3 and Table 4 above, additional treatment related adverse effects may be observed with further experience. For a description of the adverse effects of irinotecan please refer to the full prescribing information [16].

2.1.6 MM-398 PK in Humans

The pharmacokinetic profile of MM-398 single agent was investigated in a phase I clinical study (PEP0201) in patients at 60, 120 or 180 mg/m^2 and in a phase II 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 (Cmax) ranged from 48-79 µg/ml for 120 mg/ m^2 of MM-398, which was approximately 50 fold higher than 125mg/ m^2 free irinotecan. The total irinotecan half-life (t1/2) for MM-398 ranged from 21 to 48 hours which was approximately 2-3 fold higher than 125 mg/ 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, SN-38 Cmax levels at 120 mg/ m^2 of MM-398 ranged from 9 to 17 ng/ml, which was approximately 50% less than free irinotecan at 125 mg/ m^2. Overall exposure of SN-38 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 300 mg/ m^2. For both SN-38 and total irinotecan, AUC increases less than proportionally with dose of MM-398. The PK parameters of encapsulated irinotecan almost matched that of total irinotecan indicates 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. Table 5 and Table 6 below summarize the PK findings in previous studies of MM 398.

Table 5: MM-398 PK in Q3W Regimen (Irinotecan, Liposome + Free Drug)

Study	PEP0203				PEP0201		PEP0206		Camptosar® Package Insert	
Drug	MM-398							Camptosar®		
Dose (mg/m^2)	60 (n=3)	80 (n=6)	100 (n=4)	120 (n=2)	120 (n=6)	180 (n=4)	120 (n=37)	300 (n=27)	125 (n=64)	340 (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 (± 16.8)	32.09 (± 18.2)	48.11 (± 17.4)	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)	1,177 (± 308)	2,835 (± 1,817)	1,945 (± 1,029)	1,651.5 (± 1,412)	24.2 (± 7.7)	10.2 (± 3.27)	20.60 (± 6.03)
$AUC_{0-\infty}$ (µg•h/mL)	1,114 (± 1,270)	1,211 (± 924)	2,472 (± 1,261)	1,261 (± 500)	2,963 (± 1,947)	1,963 (± 1,035)	1,812.2 (± 1,602)	26.2 (± 9.0)	-	-
Cl ($L/h/m^2$)	0.1249 (± 0.1058)	0.1164 (± 0.0949)	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: AUC0-T is defined as T = 24 hours for Camptosar® package insert, T= 49.5 hours for Camptosar in the PEP0206 study and T = 169.5 hours for MM-398. Arithmetic mean and standard deviation are shown. Results are shown as arithmetic mean ± standard deviation.

Table 6: MM-398 PK in Q3W Regimen (SN-38)

Study	PEP0203				PEP0201		PEP0206		Camptosar® Package Insert	
Drug	MM-398							Camptosar®		
Dose (mg/m2)	60 n=3	80 (n=6)	100 (n=4)	120 (n=2)	120 (n=6)	180 (n=4)	120 (n=37)	300 (n=27)	125 (n=64)	340 (n=6)
Cmax (µg/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)
t1/2 (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)
AUC0-T (µg•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)
AUC0-∞ (µg•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, T= 49.5 hours for Camptosar® in the PEP0206 study and T = 169.5 hours for MM-398. Results are shown as arithmetic mean ± standard deviation.

The pharmacokinetic parameters of total irinotecan and SN-38 following the administration of 80 mg/m^2 MM-398 in the Pilot Phase of this protocol (n=13) are consistent with these previous observations. For total irinotecan, peak plasma concentrations were ~38.12 µg/ml with an elimination half-life of 24.45 h. Overall exposure at one week was 1,356 h·µg/mL. For SN-38, peak plasma concentrations were ~3.04 ng/ml. Overall exposure at one week was 179 h·ng/mL. These summary statistics are given as geometric means.

2.2 Ferumoxytol

Ferumoxytol (Feraheme™- AMAG Pharmaceuticals, Inc.) is a small (17-31 nm in diameter), non-stoichiometric magnetite (superparamagnetic iron oxide), coated with polyglucose sorbitol

carboxymethylether, nanoparticle. It is approved to treat iron deficiency anemia in patients with chronic renal failure. It is also used experimentally as an imaging agent in cancer patients [17].

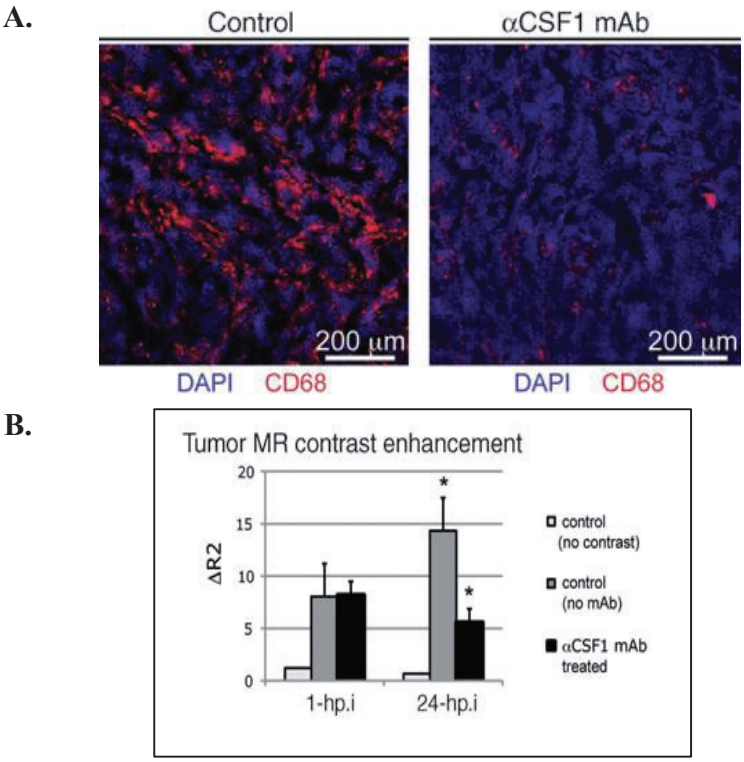
2.2.1 Use of Ferumoxytol as an Imaging Agent

One of the properties of ferumoxytol is its prolonged residence time within the intravascular space, due to an average particle size of approximately 30 nm and slow clearance from the blood stream. When performing MRI studies in patients given this agent for the treatment of their anemia, angiographic images can be obtained up to 24 hours post injection. This enhancement of the intravascular space following ferumoxytol administration has provided a novel approach to imaging pathologic conditions that involve the vascular tree, such as in stroke, vascular malformations, chronic renal disease and tumor vascularity, even in patients without kidney disease [18]. In addition, this agent has been used in patients with CNS malignancies to measure tumor vascularity and the response to chemotherapy [19]. FDA has designated this agent as an orphan drug for brain tumor imaging.

An interesting feature of this agent is that delayed MRI, after 24-72 hours post injection, results in visualization of inflammatory cells in tissue due to the eventual leakage of the agent into the interstitial space, followed by uptake of the nanoparticles into macrophages [15], [20], [21], [22].

There is early evidence that shows that TAMs take up ferumoxytol leading to distinctive signal changes which can be detected on MRI. Specifically, delayed ferumoxytol signal has been shown to cause T2* susceptibility-related signal loss (so-called T2*-signal hypo- enhancement) on T2*-weighted Gradient-Echo (GRE) images and T1 hyper-enhancement due to T1-shortening on heavily T1-weighted images in glioblastoma multiforme and in chronic renal insufficiency. This signal change correlates with the TAM population. Preclinical studies in mice have supported the possibility of utilizing ferumoxytol for MRI of TAM's [15]. Anti-CSF-1 antibody was used to deplete TAM's as evidenced by reduction in the number of CD68 positive cells (Figure 5A). A decreased MRI signal following depletion of macrophages was observed, further supporting TAM-mediated uptake of ferumoxytol (Figure 5B).

Figure 5: TAM Mediated Uptake of Ferumoxytol



(A) IHC images confirm the depletion of macrophages (CD68 cells (red)) in the MMTV-PyMT spontaneous metastatic mouse model with anti-CSF-1 antibody. (B) Ferumoxytol-enhanced MRI signal is reduced in the MMTV-PyMT spontaneous metastatic mouse model at 24 hours in mice treated with anti-CSF-1 antibody [15].

2.2.2 Potential Toxicities of Ferumoxytol

The US package insert dated 03/2015 ferumoxytol lists the following warnings and precautions: hypersensitivity reactions, hypotension, iron overload and ability to affect the diagnostic capability of MRI.

Across three randomized clinical trials that enrolled 605 patients treated with ferumoxytol, the following adverse events were reported by ≥ 1% of patients treated with ferumoxytol: nausea, dizziness, hypotension, peripheral edema, headache, edema, vomiting, abdominal pain, chest pain, cough, pruritus, pyrexia, back pain, muscle spasms, dyspnea and rash [17].

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In the initial clinical trials of Feraheme (ferumoxytol), conducted predominantly in patients with chronic kidney disease, serious hypersensitivity reactions were reported in 0.2 percent (3/1,726) of patients receiving Feraheme. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7 percent (63/1,726) of these patients. In other trials that did not include patients with chronic kidney disease, moderate to severe hypersensitivity reactions, including anaphylaxis, were reported in 2.6 percent (26/1,014) of patients treated with Feraheme.

The following serious adverse reactions have been reported from the post-marketing experience with Feraheme: fatal, life-threatening, and serious anaphylactic-type reactions, cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, unresponsiveness, loss of consciousness, tachycardia/rhythm abnormalities, angioedema, ischemic myocardial events, congestive heart failure, pulse absent, and cyanosis. These adverse reactions have usually occurred within 30 minutes after the administration of Feraheme. Reactions have occurred following the first dose or subsequent doses of Feraheme.

All IV iron products carry a risk of potentially life-threatening allergic reactions. At the time of the US approval of Feraheme in 2009, this risk was described in the Warnings and Precautions section of the drug label.

Additionally, since its approval, cases of serious hypersensitivity, including death, have been reported for Feraheme. In a post- marketing analysis performed by the FDA, a search of the FDA Adverse Event Reporting System database identified 79 cases of anaphylactic reactions associated with Feraheme administration, reported from the time of approval to June 30, 2014. Of the 79 cases, 18 were fatal, despite immediate medical intervention and emergency resuscitation attempts. The 79 patients ranged in age from 19 to 96 years. Nearly half of all cases reported that the anaphylactic reactions occurred with the first dose of Feraheme. Approximately 75 percent (60/79) of the cases reported that the reaction began during the infusion or within 5 minutes after administration completion. Frequently reported symptoms included cardiac arrest, hypotension, dyspnea, nausea, vomiting, and flushing. Of the 79 cases, 43 percent (34/79) of the patients had a medical history of drug allergy, and 24 percent had a history of multiple drug allergies.

Based on the FDA evaluation, the prescribing instructions and other label information were updated to include a Boxed Warning that describes these serious risks and recommendation for use, described further in section 6.2.4.

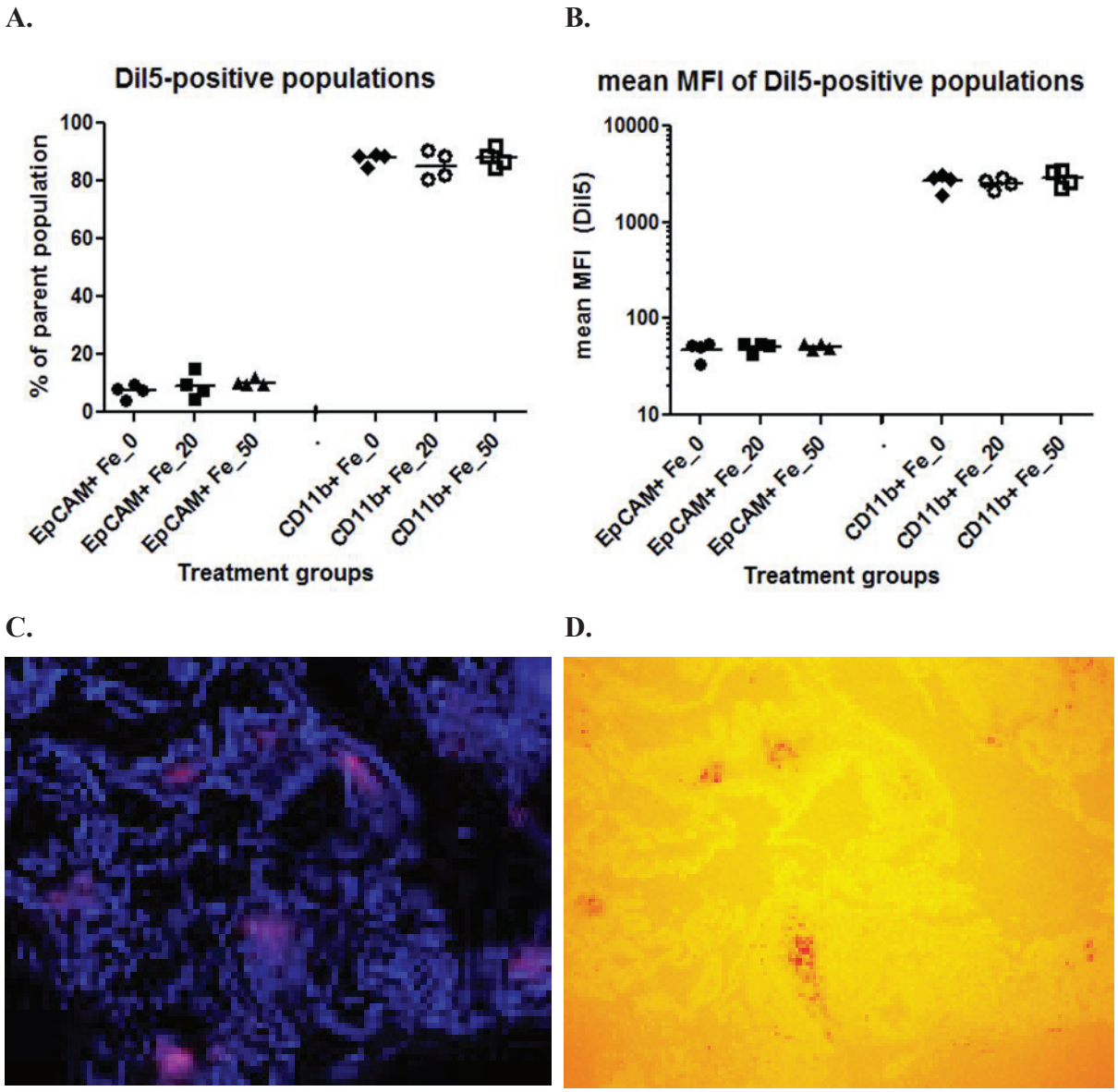
2.2.3 Interaction of Ferumoxytol and MM-398

Despite early encouraging studies with ferumoxytol in patients, little is known about the optimal conditions and timing of FMX-MRI to measure TAM. For example, the number of TAMs, timing of MRI imaging and dose of ferumoxytol infusion for optimal signal-to-noise ratios has yet to be determined. Furthermore, it is not known what specific tumor types or histologies would favor ferumoxytol imaging or what the impact tumor micro- or macro-environment would have on the ability to detect TAM signal on MRI. Pre-clinical studies with MM-398 have elucidated the role of TAMs in MM-398 intracellular tumoral accumulation a key step in the processing MM-398 into SN-38. As a consequence of this mechanism of action, there is a desire to have a way to reliably measure TAMs in a non-invasive manner. FMX-MRI may provide one such technique for addressing the role of TAMs in the treatment response to MM-398 and similar liposomal compounds. Thus, a pilot study is warranted to evaluate the role of FMX-MRI in detecting a TAM signal and correlating it to MM-398 accumulation and activation.

Preclinical studies with MM-398 suggest that TAMs are a dominant cell type internalizing MM-398, a key step in processing MM-398 into tumoral SN-38. TAMs also take up ferumoxytol which provides contrast when performing MRI of tumors. In this clinical study, we plan to image patients with metastatic tumors using ferumoxytol as the MRI contrast, followed by treatment with MM-398. Thus it was critical to evaluate whether ferumoxytol might have a negative impact on uptake of MM-398 by TAM's.

To determine the interaction between ferumoxytol and MM-398, we performed studies in HT-29 colon xenografts. Tumor bearing mice were injected with ferumoxytol, and 24 hours later with either labeled (DiI5) liposomes to assess liposome distribution (Figure 5) or MM-398 to measure tumor metabolite levels (Figure 7). Both flow cytometry and IHC analysis were performed to evaluate intratumoral localization of liposomes (Figure 6A) and alterations in overall tumor DiI5 liposome uptake (Figure 6B). We observed predominant uptake of DiI5 liposomes by tumor associated macrophages (CD11b+ cells) when compared to tumor cells (EPCAM+). Further, ferumoxytol (20 mg/kg or 50 mg/kg) did not alter the overall DiI5 liposome uptake. We also observed a spatial correlation between the intratumor accumulation of liposomes (Figure 6C) and the ferumoxytol signal within tumors (Figure 6D).

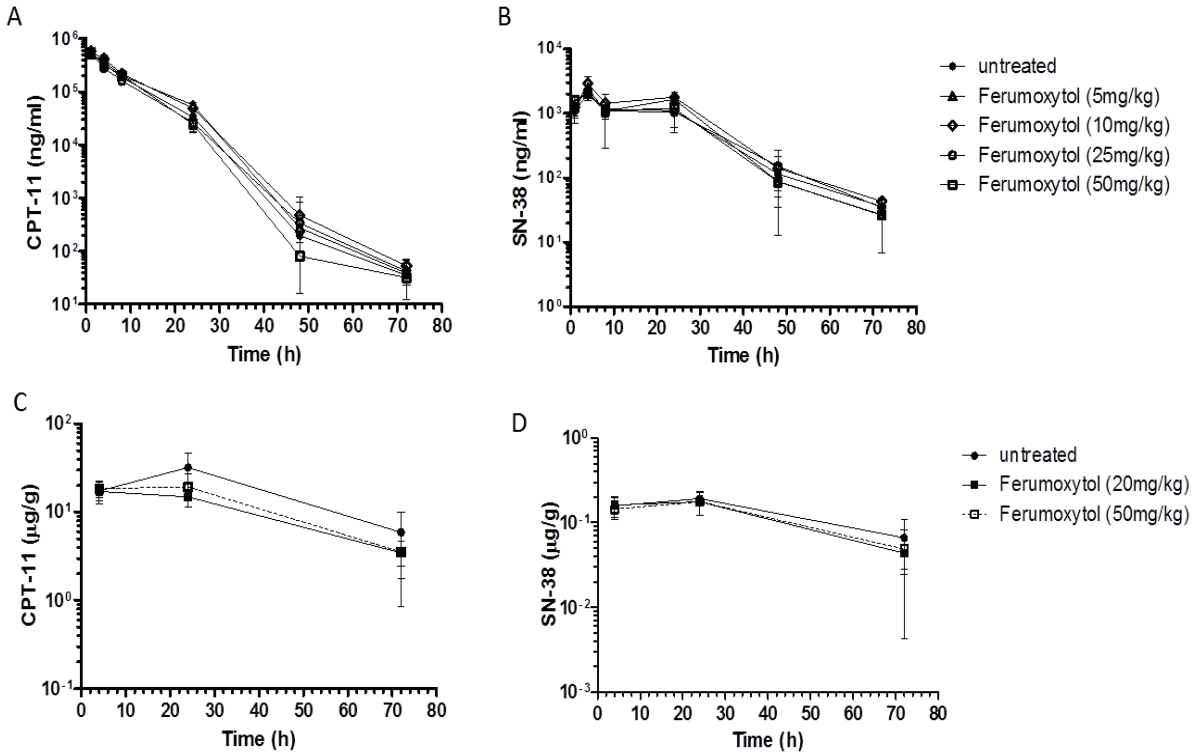
Figure 6: Uptake of Liposomes by TAMS



HT-29 tumor bearing mice were injected with ferumoxytol followed by DiI5 liposomes. FACS analysis data showed no effect of ferumoxytol (Fe) on overall DiI5 liposome uptake in either EpCAM+ tumor cells or CD11b+ myeloid cells (A). The mean fluorescence intensity (MFI) of DiI5 liposomes was higher in CD11b+ myeloid cells and remained unaltered by ferumoxytol as compared to MFI in EPCAM+ tumor cells (B). (C) IHC analysis shows clear spatial correlation between the intratumor liposomes (red) accumulation and ferumoxytol staining (Prussian blue staining) within the tumors (D)

The pharmacokinetic analysis performed using HPLC revealed unaltered levels of both irinotecan and SN-38 in plasma (Figure 7A and Figure 7B) and HT-29 tumors (Figure 7C and Figure 7D) following ferumoxytol exposure. These data clearly suggested that ferumoxytol could be used for MRI without impacting the deposition or local activation of MM-398.

Figure 7: Irinotecan and SN-38 Levels are Not Impacted by Ferumoxytol



Effects of ferumoxytol on the PK profile of MM-398 in mice in plasma (A, B) and tumor (C, D).

2.3 Summary of Study Rationale

In this study, we propose to use FMX-MRI in patients being treated with MM-398 to both determine the imaging parameters that could be applied to future clinical trials and to better define the appropriate strategy for incorporating ferumoxytol in TAM imaging for MM-398 studies. Having a biomarker for TAMs would further assist in understanding TAM-tumor biology interactions and provide insight into which treatments may rely upon or be impeded by these inflammatory cells. Additionally, as the size of ferumoxytol is relatively large (17-31 nm), the delivery of ferumoxytol to the tumor microenvironment may serve as a surrogate for the tumor delivery and deposition of MM-398 liposomes. Therefore, the Expansion Phase will evaluate FMX-MRI and tumor lesion ferumoxytol signal as a tool for predicting response to treatment with MM-398 in patients with locally advanced or metastatic breast cancer.

An important goal of the Expansion Phase of this study is to assess multi-institutional feasibility of imaging with FMX-MRI with the purpose of correlating clinical activity in a specific patient population with uptake of ferumoxytol as measured by MRI. Advanced breast cancer has been selected for the study based on published clinical data on irinotecan and preliminary evidence of clinical activity with MM-398 as described below.

Irinotecan has a distinct mechanism of action from other drugs commonly used to treat patients with metastatic breast cancer and limited cross-resistance [32]. Irinotecan is used to treat patients with advanced breast cancer with single agent response rates of 5-23% [38]. Results for single agent irinotecan signal the need for both an improved irinotecan-based agent as well as biomarker strategy to identify patients likely to respond. We believe that MM-398 and FMX-

MRI have potential to fill this role. In previous clinical studies (PEP0201, PEP0203) 6 patients with metastatic breast cancer have been treated with MM-398, alone or in combination with 5-FU/LV. Two patients achieved stable disease and 1 patient achieved a partial response as best response.

3 Study Objectives

3.1 Primary Objectives

Pilot Phase (Completed)

In patients with NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma or head and neck cancer, who are undergoing therapy with MM-398:

- To evaluate the feasibility of delayed ferumoxytol MRI (FMX-MRI) to identify tumor associated macrophages (TAMs)
- To measure tumor levels of irinotecan and SN-38

Expansion Phase:

In patients with locally advanced or metastatic breast cancer:

- To further investigate the feasibility of ferumoxytol (FMX) quantitation in tumor lesions
- To characterize the relationship between ferumoxytol (FMX) tumor uptake and tumor response to MM-398

3.2 Secondary Objectives

All Phases:

- To characterize the safety profile of MM-398 in the presence of FMX
- To assess tumor response to treatment
- To characterize the pharmacokinetics (PK) of MM-398

Pilot Phase (Completed):

- To estimate the correlations between FMX-MRI, TAM levels, and tumor levels of irinotecan and SN-38 with administration of MM-398
- To determine the value of FMX-MRI in directing tissue biopsy

Expansion Phase:

- To characterize the efficacy of MM-398 in patients with locally advanced or metastatic breast cancer using key efficacy indicators such as objective response rate and clinical benefit rate
- To assess the association between deposition, as visualized by ferumoxytol imaging, and measures of efficacy
- To further characterize the safety profile of MM-398, in the presence of FMX, in patients with metastatic breast cancer
- To assess the analytical performance of FMX-MRI measurements and optimize FMX-MRI parameterization

3.3 Exploratory Objectives

Pilot Phase (Completed):

- To estimate the correlations between potential pharmacodynamic (PD) markers (FMX-MRI, TAM, tumor irinotecan, tumor SN-38 levels) and safety
- To estimate the correlations between potential PD markers (FMX-MRI, TAM, tumor irinotecan, tumor SN-38 levels) and tumor response
- To characterize each tumor biopsy to permit multivariate comparative analyses between tumor characteristics, FMX-MRI signal and drug metabolite levels

Expansion Phase:

- To evaluate a set of potential biomarkers from tumor tissue and blood samples for their ability to predict PK and/or response to MM-398 treatment

4 Study Design

4.1 Indications and Number of Patients

This study will enroll approximately 12 patients, up to 20 in total in the Pilot Phase. The first three patients that are enrolled in this phase can have any solid tumor type; however subsequent patients must have NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, gastroesophageal junction adenocarcinoma or head and neck cancer. No more than three patients with ER/PR positive breast cancer can be enrolled in the Pilot Phase and similar restrictions may be placed on other tumor types to ensure a heterogeneous population.

These indications were selected based on data suggesting that these tumor types have high levels of CD68 (tumor associated macrophages) and carboxylesterase enzyme (CES) activity or high levels of deposition, any of which may correlate to MM-398 response.

An Expansion Phase will enroll cohorts of single indications of patients with locally advanced or metastatic breast cancer, in 3 cohorts:

Cohort 1: ER and/or PR-positive breast cancer
Cohort 2: TNBC
Cohort 3: BC with active brain metastasis

The total enrollment for the study will be approximately 45 patients.

4.2 Study Stages and Treatment Design

There are four stages to this study, defined as periods:

- Screening Period (-28d): patients undergo screening assessments to determine if they are eligible for the study
- Ferumoxytol (FMX) Period (Day 1 – Day 2): patients receive ferumoxytol (FMX) infusion and undergo required FMX-MRI scans prior to receiving MM-398.
- MM-398 Treatment Period (C1D1 – progression of disease): patients receive an MM-398 dose of 60 mg/m^2 every 2 weeks, which should be dose escalated to 80 mg/m^2 every 2 weeks in subsequent doses depending on patient tolerance, other required assessments, and undergo a post-treatment (MM-398) multiple pass core biopsy

- Follow Up Period (+30d from last dose): patients return to clinic 30 days following the last dose of MM-398 for final safety assessments

For all enrolled patients, a single dose of 5 mg/kg of ferumoxytol will be administered at Day 1 during the ferumoxytol period by intravenous infusion in 50-200 mL of 0.9% sodium chloride or 5% dextrose over a minimum period of 15 minutes following dilution. The total single dose will not exceed 510mg, the maximum approved single dose of ferumoxytol.

MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of60 mg/m^2 every two weeks. The MM-398 period (C1D1) should begin within 7 days of the ferumoxytol infusion. The dose of MM-398should be escalated to 80 mg/m^2 every two weeks depending on patient tolerance.

All patients will be treated until disease progression (see section 7.1.6.2) or unacceptable toxicity.

Enrollment and Treatment

Between 12 and 20 patients will be enrolled in this the Pilot Phase of the study. The Expansion Phase will enroll up to 30 evaluable patients, in three cohorts. The total enrollment for the study will be approximately 45 patients.

Patients receiving ferumoxytol and not completing all assessments and/or those who do not have evaluable FMX MR images, may still proceed to the MM-398 treatment phase; however additional patients may be enrolled to ensure that adequate MRI data are collected to achieve the objectives of the study. In addition, in order to be considered evaluable from a pharmacodynamic standpoint for the Expansion Phase, patients must have received MM-398 and completed at least one CT scan at the 8-week post-treatment time point.

5 Patient Selection and Discontinuation

5.1 Inclusion Criteria

For inclusion into the study, patients must have/be:

All Phases

a) Pathologically confirmed solid tumors that have recurred or progressed following standard therapy, or that have not responded to standard therapy, or for which there is no standard therapy, or who are not candidates for standard therapy
    1. Pilot Phase (Completed): the first three patients enrolled may have any solid tumor type, however patients subsequently enrolled into the Pilot phase must have one of the following tumor types: NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma or head and neck cancer.
    2. Expansion Phase: the following invasive breast cancer tumor sub-types are required:
        i. Cohorts 1 and 2 must be documented to be HER2 negative as outlined in the ASCO/CAP 2013 guidelines for HER2 testing, defined by at least one of the following:
            - HER2 immunohistochemistry (IHC) staining of 0 or 1+,

OR if HER2 IHC 2+

- Negative by In-Situ Hybridization (ISH) based on defined as a Single-probe average HER2 copy number <4.0 signals/cell
- OR Negative by Dual-probe ISH defined as a HER2/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell

ii. In addition, breast cancer patients must patients must be

- **Cohort 1:** hormone receptor positive breast cancer patients with ER-positive and/or PR-positive tumors defined as ≥1% of tumor nuclei that are immunoreactive for ER and/or PR and HER2 negative
- **Cohort 2:** triple negative breast cancer (TNBC) patients with ER-negative, PR-negative tumors defined as <1% of tumor nuclei that are immunoreactive for ER and PR and HER2 negative
- **Cohort 3:** Any sub-type of metastatic breast cancer and active brain metastases (see additional criteria o-r below)

b) Documented metastatic disease with at least 1 radiologically measurable lesion as defined by RECIST v1.1 (except Cohort 3, see inclusion criterion o below)
c) ECOG performance status 0 or 1
d) Bone marrow reserves as evidenced by:
   - ANC > 1,500 cells/µl without the use of hematopoietic growth factors
   - Platelet count > 100,000 cells/µl
   - Hemoglobin > 9 g/dL
e) Adequate hepatic function as evidenced by:
   - Normal serum total bilirubin
   - AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present)
f) Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN
g) Normal ECG or ECG without any clinically significant findings
h) Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy
i) At least 18 years of age
j) Able to understand and sign an informed consent (or have a legal representative who is able to do so)

<u>Expansion Phase additional inclusion criteria:</u>

k) Received at least one cytotoxic therapy in the metastatic setting, with exception of TNBC patients who progressed within 12 months of adjuvant therapy
l) Received ≤ 5 prior lines of chemotherapy in the metastatic setting (no limit to prior lines of hormonal therapy in Cohort 1)
m) Candidate for chemotherapy
n) At least one lesion amenable to multiple pass biopsy (exception: Cohort 3 patients)

Expansion Phase **Cohort 3** additional inclusion criteria:

o) Radiographic evidence of new or progressive brain metastases after prior radiation therapy with at least one brain metastasis measuring ≥ 1 cm in longest diameter on gadolinium-enhanced MRI (note: progressive brain lesions are not required to meet RECIST criteria in order to be eligible; extra-cranial metastatic disease is also allowed)
p) Imaging following prior radiation is not consistent with pseudo-progression in the judgment of treating clinician
q) Neurologically stable as defined by:
   - Stable or decreasing dose of steroids and anti-convulsants for at least 7 days prior to study entry
   - No clinically significant mass effect, hemorrhage, midline shift, or impending herniation on baseline brain imaging
   - No significant focal neurologic signs and/or symptoms which would necessitate radiation therapy or surgical decompression in the judgment of the treating clinician
r) No evidence of diffuse leptomeningeal disease on brain MRI or by previously documented cerebrospinal fluid (CSF) cytology-NOTE: discrete dural metastases are permitted.

5.2 Exclusion Criteria

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

18. Active central nervous system metastases, indicated by clinical symptoms, cerebral edema, or steroid requirement (applies to Pilot Phase and Expansion Phase Cohorts 1-2 only)

s) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1
t) Have received irinotecan or bevacizumab (or other anti-VEGF therapy) within the last six months; and for Expansion Phase patients, have received any prior treatment with a Topo1 inhibitor (irinotecan-derived or topotecan)
u) History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years.
v) Unable to undergo MRI due to presence of errant metal, cardiac pacemakers, pain pumps or other MRI incompatible devices
w) A history of allergic reactions to compounds similar to ferumoxytol as described in full prescribing information for ferumoxytol injection, or to other IV iron replacement products (e.g. parenteral iron, dextran, iron-dextran, or parenteral iron polysaccharide preparations)
x) Documented history of allergies to multiple drugs
y) Known hypersensitivity to any of the components of MM-398, or other liposomal products
z) Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease
   - Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion

- NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

19. 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
20. Prior chemotherapy administered within 3 weeks, or within a time interval less than at least 5 half-lives of the agent, whichever is longer, prior to the first scheduled day of dosing in this study
21. Received radiation therapy in the last 14 days
22. Evidence of Iron overload as determined by:
    - Fasting transferrin saturation of >45 % and/or
    - Serum ferritin levels >1000 ng /ml
23. Treated with parenteral iron in the previous 4 weeks
24. HIV-positive patients on combination antiretroviral therapy or other conditions requiring treatment where there is a potential for ferumoxytol to have negative pharmacokinetic interactions
25. 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
26. 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.

5.3 Patient Discontinuation

Patients may withdraw or be withdrawn from the study at any time and for any reason. Some possible reasons for early withdrawal include, but are not limited to the following:

- Progressive neoplastic disease
- The patient experiences an adverse event which, in the opinion of the Investigator, precludes further participation in the trial
- Clinical and/or symptomatic deterioration
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
- Noncompliance with the protocol
- Withdraws consent
- The Investigator removes the patient from the trial in the best interests of the patient
- Study termination by the Sponsor
- Use of prohibited concomitant medications
- Lost to follow up

If a patient withdraws from the trial, attempts should be made to contact the patient to determine the reason(s) for discontinuation.

All procedures and evaluations required by the 30 day follow up visit should be completed when a patient is discontinued. All patients who discontinue the trial as a result of an adverse event must be followed until resolution or stabilization of the adverse event.

5.4 Patient Replacement

The following patients will not be considered pharmacodynamically evaluable for the Expansion Phase of the study and may be replaced at the discretion of the Sponsor.

- Patients who do not complete all study procedures during the FMX phase and/or who do not have evaluable FMX MR images
- Patients who discontinue the study early, prior to completing the 8-week disease evaluation

6 Investigational Product and Study Treatment

6.1 Description of MM-398

MM-398 is irinotecan (also known as CPT-11) encapsulated in a nanoliposomal drug delivery system in the form of the sucrose octasulfate salt of irinotecan. It will be supplied as sterile, single-use vials containing 10 mL of MM-398 at a concentration of 5 mg/mL. The vials contain a 0.5 mL excess to facilitate the withdrawal of the label amount from each vial.

6.1.1 Storage and Handling of MM-398

MM-398 must be stored refrigerated at 2 to 8°C, with protection from light. Light protection is not required during infusion. MM-398 must not be frozen. Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe. They must contact the Sponsor or its designee if they notice a problem with the study drug.

MM-398 must be diluted prior to administration. The diluted solution is physically and chemically stable for 4 hours at room temperature (15-30°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 4 hours if kept at room temperature (15-30°C).

6.1.2 Packaging and Labeling of MM-398

Twenty vials of MM-398 will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with local regulatory requirements.

6.1.3 Administration of MM-398

MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of60 mg/m^2 every two weeks. The dose of MM-398 should be escalated to 80 mg/m^2 every two weeks depending on patient tolerance. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.

Prior to administration, the appropriate dose of MM-398 must be diluted in 5% Dextrose Injection solution (D5W) to a final volume of 500 mL. Care should be taken not to use any

diluents other than D5W or 0.9% sodium chloride USP, to a final volume of 500 mL. MM-398 can be administered using standard intravenous administration bags and tubing.

The actual dose of MM-398 to be administered will be determined by calculating the patient's body surface area (BSA) at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since MM-398 vials are single use vials, site staff must not store any unused portion of a vial for future use and must discard all unused portions of the product.

If a patient experiences an infusion reaction, or any adverse event deemed as related by the investigator to ferumoxytol, MM-398 should be held until the event is grade 1 or resolved.

6.1.4 Premedication Prior to MM-398 Administration

All patients must be premedicated prior to MM-398 infusion with standard doses of dexamethasone and a 5-HT3 antagonist or other anti-emetics according to standard institutional practices for irinotecan administration. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

6.1.5 Important Treatment Considerations After MM-398 Administration

Data from previous MM-398 studies does not show any unexpected toxicity when compared to the active ingredient, irinotecan, which has been studied extensively. The warnings and precautions for the use of irinotecan and the treatment procedures for managing those toxicities are provided below.

6.1.5.1 Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who experienced early cholinergic symptoms during the previous cycle of MM-398, prophylactic administration of atropine will be given at the discretion of the investigator.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide, as described in section 6.4.3 (Therapy for Diarrhea). Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

6.1.5.2 Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia at the investigator's discretion, provided it is administered within parameters specified in section 6.4.2. Patients, who are known to have

experienced Grade 3 or 4 neutropenia while receiving prior anti-neoplastic therapy, should be monitored carefully and managed as outlined in section 6.1.6.1

6.1.5.3 Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

6.1.5.4 Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support.

6.1.5.5 Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan- containing regimens; the specific cause of these events has not been determined.

6.1.5.6 Pregnancy

The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known.

6.1.5.7 Care of Intravenous Site

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile saline and applications of ice are recommended.

6.1.5.8 Patients at Particular Risk

In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

6.1.5.9 Acute Infusion Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications.

6.1.5.10 Other Potential Toxicities

MM-398, the liposomal formulation of irinotecan is different from irinotecan in unencapsulated formulation, so there is a potential for toxicities other than those caused by irinotecan. All patients should be monitored closely for signs and symptoms indicative of drug toxicity,

particularly during the initial administration of treatment. QTc prolongation that occurs in the setting of diarrhea induced electrolyte imbalance should be treated by with appropriate electrolyte repletion. Once the underlying abnormality is corrected and the ECG abnormalities have reversed, treatment may continue under careful monitoring and with appropriate dose modification for diarrhea as described above.

6.1.6 Dose Reductions Due to Toxicity

The toxicity of each cycle must be recorded prior to the administration of a subsequent cycle and graded according to the NCI CTCAE (Version 4.02). All dose reductions should be based on the worst preceding toxicity.

Dosing may be held for up to 2 weeks from the occurrence to allow for recovery from toxicity related to the study treatment. If the time required for recovery from toxicity is more than 2 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor regarding risks and benefits of continuation.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

6.1.6.1 Hematologic Toxicities

Prior to each MM-398 dosing, patients must have:

- ANC $\geq 1500/mm^3$
- Platelet count $\geq 100{,}000/mm^3$

Treatment should be delayed to allow sufficient time for recovery, and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to $\geq 1500/mm^3$ and the patient must have recovered from infection.

Table 7: MM-398 Dose Modifications for Neutrophil Count

Worst CTCAE Grade	ANC Levels (cells/mm^3)	Modification		
		Occurrence	MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)	MM-398 adjustment in patients receiving 80 mg/m^2 (if dose escalated from 60 mg/m^2)
Grade 1 or 2	1000-1999	Any	Same as previous dose	Same as previous dose
Grade 3 or 4	<1000	First	50 mg/m^2	60 mg/m^2
		Second	40 mg/m^2	50 mg/m^2
		Third	Discontinue from MM-398	Discontinue from MM-398

Table 8: MM-398 Dose Modifications for Other Hematologic Toxicities

Worst CTCAE Grade	Modification		
	Occurrence	MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)	MM-398 adjustment in patients receiving 80 mg/m^2 (if dose escalated from 60 mg/m^2)
Grade 1 or 2	Any	Same as previous dose	Same as previous dose
Grade 3 or 4	First	50 mg/m^2	60 mg/m^2
	Second	40 mg/m^2	50 mg/m^2
	Third	Discontinue from MM-398	Discontinue from MM-398

6.1.6.2 Non-hematologic Toxicities

Treatment should be delayed until diarrhea resolves to < Grade 1, and for other Grade 3 or 4 non-hematological toxicities, until they resolve to Grade 1 or baseline. Guidelines for dose adjustment of MM-398 for drug related diarrhea and other Grade 3 or 4 non-hematological toxicities are provided below.

Table 9: MM-398 Dose Modifications for Diarrhea

Worst CTCAE Grade	Modification		
	Occurrence	MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)	MM-398 adjustment in patients receiving 80 mg/m^2 (if dose escalated from 60 mg/m^2)
Grade 1 or 2	Any	Same as previous dose	Same as previous dose
Grade 3 or 4	First	50 mg/m^2	60 mg/m^2
	Second	40 mg/m^2	50 mg/m^2
	Third	Discontinue from MM-398	Discontinue from MM-398

Table 10: MM-398 Dose Modifications for Non-hematologic Toxicities Other Than Diarrhea, Asthenia and Grade 3 Anorexia

Worst CTCAE Grade	Modification		
	Occurrence	MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)	MM-398 adjustment in patients receiving 80 mg/m^2 (if dose escalated from 60 mg/m^2)
Grade 1 or 2	Any	Same as previous dose	Same as previous dose
Grade 3 or 4 (except nausea and vomiting)	First	50 mg/m^2	60 mg/m^2
	Second	40 mg/m^2	50 mg/m^2
	Third	Discontinue from MM-398	Discontinue from MM-398
Grade 3 or 4 nausea and/or vomiting[a]	First	50 mg/m^2	60 mg/m^2
	Second	40 mg/m^2	50 mg/m^2
	Third	Discontinue from MM-398	Discontinue from MM-398

[a] For Grade 3 or 4 nausea and vomiting, dose reduce only if they occur despite optimal anti-emetic therapy

6.1.6.3 UGT1A1*28 Homozygous Patients

Patients will be tested for UGT1A1*28 status at screening. The result of the test is not required prior to the initial dose of MM-398. Both the starting dose and dose modifications for toxicities will be the same for all patients regardless of UGT1A1*28 genotype.

6.1.7 Management of Infusion Reactions to MM-398

Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.02) definition of an allergic reaction/hypersensitivity as defined below:

Grade 1: Transient flushing or rash, drug fever < 38° C (< 100.4°F); intervention not indicated
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <= 24 hrs.
Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Grade 1
- Slow infusion rate by 50%
- Monitor patient every 15 minutes for worsening of condition

Grade 2
- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor patient every 15 minutes for worsening of condition
- For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

Grade 3
- Stop infusion and disconnect infusion tubing from patient
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary
- No further treatment with MM-398 will be permitted

Grade 4
- Stop the infusion and disconnect infusion tubing from patient
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV
- Consider hospital admission for observation
- No further treatment with MM-398 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), at the discretion of the Investigator.

For patients who experience a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally or as per institutional guidelines.

6.2 Description of Ferumoxytol

Ferumoxytol is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease. Although not approved as an indication, ferumoxytol has also been used as an imaging agent in cancer patients and will be utilized as such in this study as opposed to an iron replacement product.

6.2.1 Storage and Handling of Ferumoxytol

Ferumoxytol must be stored at controlled room temperature (20° to 25°C [68° to 77°F]). Excursions to 15° – 30°C (59° – 86°F) are permitted.

6.2.2 Packaging and Labeling of Ferumoxytol

Ferumoxytol (30 mg/mL) is available for intravenous injection in single use vials. Each vial contains 510 mg of elemental iron in 17 mL. Ferumoxytol will be provided to the patient by the hospital pharmacy commercial supply or by individual patient prescription.

6.2.3 Administration of Ferumoxytol

A single dose of ferumoxytol will be administered at Day 1 by intravenous infusion. This dosing schedule is less intense than the approved label, which recommends two doses of 510 mg 3 to 8 days apart; however, since ferumoxytol is being used as imaging agent in this study as opposed to a replacement product for iron deficiency, a lower dose is more appropriate.

Dosing will be calculated according to patient weight at 5 mg/kg. The total single dose will not exceed 510 mg, the maximum approved single dose of ferumoxytol. Care should be taken to review and follow the ferumoxytol package insert for safety precautions.

Do not administer ferumoxytol by undiluted IV injection. This product should be diluted per label instructions. Ferumoxytol should only be administered as an IV infusion in 50-200 mL of 0.9% sodium chloride or 5% dextrose over a minimum period of 15 minutes following dilution.

Administer while patient is in a reclined or semi-reclined position. Patients should be closely monitored for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during administration and for at least 30 minutes following each infusion as per the ferumoxytol label instructions.

If a patient experiences an adverse reaction of grade 2 or above that is related to ferumoxytol, dosing of MM-398 should be held until the event is grade 1 or completely resolved. Any grade 2 or higher reactions possibly related to ferumoxytol should be reported to the study sponsor within 24 hours of administration.

Additional Information for Health Care Professionals

- Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving ferumoxytol. Initial symptoms may include hypotension, syncope, unresponsiveness, and cardiac/cardiorespiratory arrest with or without signs of rash.
- All intravenous (IV) iron products carry a risk of anaphylaxis; therefore, these products should be administered only in patients who require IV iron therapy. Ferumoxytol is only approved for use in adults with iron-deficiency anemia in the setting of chronic kidney disease.
- Ferumoxytol is contraindicated in patients with a history of hypersensitivity to ferumoxytol or any other IV iron product.

- Only administer ferumoxytol and other IV iron products when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.
- Patients with a history of multiple drug allergies may have a greater risk of anaphylaxis with parenteral iron products. Carefully consider the potential risks and benefits before administering ferumoxytol to these patients.
- Elderly patients 65 years of age and older with multiple or serious comorbidities who experience hypersensitivity reactions or hypotension or both following administration of ferumoxytol may have more severe outcomes.
- Advise patients to immediately report any signs and symptoms of hypersensitivity that may develop during and following ferumoxytol administration, such as respiratory distress, hypotension, dizziness or lightheadedness, edema, rash, or itching. Advise patients to seek immediate medical attention if these signs and symptoms occur.
- Allow at least 30 minutes between administration of ferumoxytol and administration of other medications that could potentially cause serious hypersensitivity reactions or hypotension or both, such as chemotherapeutic agents or monoclonal antibodies.

6.2.4 Important Treatment Considerations With Ferumoxytol

Iron levels will be measured in the blood prior to ferumoxytol administration. As currently recommended by the American Association of liver Disease, screening for iron overload is diagnosed by measuring a fasting morning transferrin saturation ≥ 45% (ratio of serum iron divided by the serum total iron binding capacity and expressed as a percentage). A ferritin level of 1000 ng/ml is likely to be also associated with organ damaging levels of iron. Both measurement of transferrin saturation and serum ferritin can be altered by inflammation as occurs in malignancy, and may be difficult to interpret. Actual tissue measurement of liver iron is the gold standard for diagnosing iron overload but is associated with some morbidity. Careful interpretation of iron test preferably with an expert is recommended.

For this protocol, a specific Adverse Event of Special Interest (AESI) includes notification and collections of any hypersensitivity reactions associated with the administration of ferumoxytol and will follow Serious Adverse Event notification procedures. Hypersensitivity reaction reports including anaphylaxis/ anaphylactoid reactions should include individual signs and symptoms, time to onset, time to resolution and any intervention or medication given for the treatment thereof.

Additional Information for Health Care Professionals

- Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving ferumoxytol. Initial symptoms may include hypotension, syncope, unresponsiveness, and cardiac/cardiorespiratory arrest with or without signs of rash.
- All intravenous (IV) iron products carry a risk of anaphylaxis; therefore, these products should be administered only in patients who require IV iron therapy. Ferumoxytol is only approved for use in adults with iron-deficiency anemia in the setting of chronic kidney disease.
- Ferumoxytol is contraindicated in patients with a history of hypersensitivity to ferumoxytol or any other IV iron product.

- Only administer ferumoxytol and other IV iron products when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.
- Patients with a history of multiple drug allergies may have a greater risk of anaphylaxis with parenteral iron products. Carefully consider the potential risks and benefits before administering ferumoxytol to these patients.
- Elderly patients 65 years of age and older with multiple or serious comorbidities who experience hypersensitivity reactions or hypotension or both following administration of ferumoxytol may have more severe outcomes.
- Advise patients to immediately report any signs and symptoms of hypersensitivity that may develop during and following ferumoxytol administration, such as respiratory distress, hypotension, dizziness or lightheadedness, edema, rash, or itching. Advise patients to seek immediate medical attention if these signs and symptoms occur.
- Allow at least 30 minutes between administration of ferumoxytol and administration of other medications that could potentially cause serious hypersensitivity reactions or hypotension or both, such as chemotherapeutic agents or monoclonal antibodies.

6.3 Drug Accountability

The Investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of MM-398. A record of all vials of study drug received and administered will be maintained on an investigational drug inventory form provided by the Sponsor. The following information will be recorded:

- Date and quantity of study drug received
- Date and quantity of study drug dispensed from the pharmacy per patient
- Date and quantity of study drug administered to each patient
- Date and quantity of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)
- Date and quantity of study drug returned to sponsor

Each shipment of study drug will contain an invoice describing the amount of drug shipped to the investigational site. The information on the invoice will be verified against the actual amount of drug received, after which the Investigator or the Investigator's designee will place the invoice in the Investigator's file.

At each monitoring visit, the Sponsor's monitor will reconcile the information on the investigational drug inventory form with the actual amount of study drug remaining at each site. At the conclusion of the study, the monitor will package and ship all unused vials of study drug back to Sponsor for destruction. Following use, empty vials of study drug may be destroyed according to local regulatory and environmental requirements. A record of any such destruction will be placed in the Investigator's file.

6.4 Concomitant Therapy

All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary. Glucocorticoids and anti-seizure medication is permitted for patients with brain metastases (Expansion Phase Cohort 3; see restrictions on anti-convulsants in section 6.5

below). Although warfarin-type anticoagulant therapies are permitted, careful monitoring of coagulation parameters is imperative, in order to avoid complications of any possible drug interactions. All concomitant medications, including transfusions of blood products, will be recorded on the appropriate case report form.

Guidelines for treating certain medical conditions are discussed below; however, institutional guidelines for the treatment of these conditions may also be used. The concomitant therapies that warrant special attention are discussed below.

6.4.1 Antiemetic Medications

Dexamethasone and a 5-HT3 blocker (e.g., ondansetron or granisetron) will be administered to all patients as premedications unless contraindicated for the individual patient. Antiemetics will also be prescribed as clinically indicated during the study period.

6.4.2 Granulocyte Colony Stimulating Factors

Use of granulocyte colony-stimulating factors (G-CSF) is permitted to treat patients with neutropenia or neutropenic fever; prophylactic use of G-CSF will be permitted only in those patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy or have had documented grade 3 or 4 neutropenia or neutropenic fever while receiving prior anti-neoplastic therapy.

6.4.3 Therapy for Diarrhea

Acute diarrhea and abdominal cramps, developing during or within 24 hours after MM-398 administration, may occur as part of a cholinergic syndrome. The syndrome will be treated with atropine. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms during the study.

Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Diarrhea should be managed according to institutional guidelines, or according to the guidelines developed by an ASCO panel for treating chemotherapy-induced diarrhea, abstracted below [23].

Table 11: Recommendations for Management of Chemotherapy Induced Diarrhea

Clinical Presentation	Intervention
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea): continue until diarrhea-free for ≥ 12 hours
Diarrhea persists on loperamide for > 24 hours	Oral fluoroquinolone x 7 days
Diarrhea persists on loperamide for > 48 hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC < 500 cells/μL, regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

6.5 Prohibited Therapy

The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John's Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and

verapamil. Treatment with these agents and any other that interact with irinotecan, should be avoided wherever possible.

Thus, the following therapies are not permitted during the trial:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or other antibodies
- Potentially curative radiotherapy; palliative radiotherapy is permitted
- Any other investigational therapy is not permitted

7 Study Procedures

7.1 Clinical Procedures

7.1.1 Medical History

Medical history will include all pertinent prior medical conditions, surgeries or other medical procedures.

7.1.2 Physical Examination

Physical examination will include a careful assessment of all body systems, including the skin; central and peripheral nervous system; eyes, ears, nose and throat; respiratory and cardiovascular systems; abdomen and extremities. Particular attention should be made to areas of possible neoplastic involvement.

7.1.3 Vital Signs

Vital signs will include weight, resting blood pressure, pulse, respiratory rate and temperature.

7.1.4 ECOG Performance Score

The Eastern cooperative oncology group (ECOG) Performance Score will be obtained by the PI or his/her designee by questioning the patient about their functional capabilities.

7.1.5 ECG

A 12 lead ECG will include a description of the cardiac rate, rhythm, interval durations and an overall impression.

7.1.6 Disease Evaluation

Tumor response will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or modified RECIST criteria (for CNS disease only; Cohort 3), to establish disease progression by computed tomography (CT) or MRI. At baseline, all Expansion Phase patients with extracranial disease will also have a standard fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT scan in order to identify lesions that are metabolically active; follow-up PET/CT scans are not required. In addition, other radiographic or scintigraphic procedures (such as radionuclide bone scans), as deemed appropriate by the Investigator, will be performed to assess sites of neoplastic involvement. The same method of assessment must be used throughout the study. Patients in Cohort 3 with both CNS and non-CNS disease will have separate evaluations of each disease type. Investigators should select target and non-target lesions in accordance with RECIST v1.1 guidelines, or modified RECIST criteria as specified below for brain lesions. Follow up measurements and overall response should also be in accordance with these guidelines, unless otherwise specified below (Cohort 3 only).

7.1.6.1 Modified RECIST Criteria for Cohort 3

Tumor response for CNS disease will be evaluated according to modified RECIST criteria as described previously [37], and as specified below. A maximum of five target lesions (≥ 5 mm in size of long axis, with at least one lesion measuring ≥ 1 cm) will be identified at baseline, with the remaining lesions followed as non-target lesions. Selection of necrotic or cystic lesions as target lesions should be avoided if other solid lesions are present. All target lesions should be measured for each follow-up disease evaluation, even if lesion size decreases to < 5 mm. If a lesion is too small to measure, a default value of 3 mm should be used. Table 12 describes the definition of response for CNS disease only; non-CNS disease will be assessed separately according to RECIST v1.1.

Table 12: CNS Response Assessment for Cohort 3

Response	Definition
Complete Response (CR)	Disappearance of all target and non-target lesions; or lesions do not show any gadolinium enhancement and are completely necrotic
Partial Response (PR)	≥ 30% decrease in the sum longest dimension (LD) of target lesions (taking as reference the baseline sum diameters) *and* an absolute decrease of at least 5 mm in at least one target lesion; non-target lesions do not meet the criteria for PD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study; non-target lesions do not meet the criteria for PD
Progressive Disease (PD)	≥ 20% increase in the sum LD of target lesions (taking as reference the *smallest sum on study*, including the baseline sum if that is the smallest on study) *and* an absolute increase in size of at least 5 mm in at least one target lesion, *or* the appearance of one or more new lesions of at least 6 mm in size; and/or growth of non-target lesion(s) sufficient to determine unequivocal progression

7.1.6.2 Criteria for Treatment Termination due to Progressive Disease

Pilot Phase and Expansion Phase patients in Cohorts 1 and 2 will be discontinued from study treatment due to progressive neoplastic disease, assessed by RECIST v1.1 as described in section 7.1.6 above. Patients in Expansion Phase Cohort 3 will have CNS and non-CNS disease assessed separately. Patients in Cohort 3 should be discontinued from study treatment for radiographic evidence of progressive disease (PD) in the CNS (see Table 12), however, patients may stay on study treatment at the Investigator's discretion for the following reasons:

- Radiographic evidence of non-CNS PD only (no evidence of CNS PD)
- Symptomatic progression of CNS disease (without radiographic evidence of PD)

If there is evidence that a patient in Expansion Phase Cohort 1 or Cohort 2 experiences PD yet has also derived clear clinical benefit from study treatment, then the Investigator, Medical Monitor and Sponsor may review the specifics of the case at the request of the Investigator. Such a patient may remain on study if the consensus judgment is that continued treatment is in the patient's best interest.

7.2 Laboratory Procedures

7.2.1 Complete Blood Count

A complete blood count will include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

7.2.2 Serum Chemistry

Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, uric acid, total protein, albumin, calcium, magnesium and phosphate. Iron levels (ferritin, iron and transferrin saturation) will be measured at the screening visit, at the time of the first MM-398 dose of Cycle 2 (first additional cycle) and at the 30 Day Follow-up visit.

7.2.3 Biomarker Samples

Whole blood and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to MM-398, and MM-398 PK. Examples of potential analyses include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), enzyme levels (e.g. MMP9).

7.2.4 Coagulation Profile

A coagulation profile will include a partial thromboplastin time and an international normalized ratio.

7.2.5 UGT1A1*28

A whole blood sample will be collected from all patients at baseline to test for UGT1A1*28 allele status. The result is not needed prior to the initial dose of MM-398. Both the starting dose and dose modifications for toxicities will be the same for all patients regardless of UGT1A1*28 genotype, as described in section 6.1.6.3.

7.2.6 Urinalysis

A urinalysis will include descriptions of color and clarity; pH; specific gravity; and analyses of blood, glucose, ketones and total protein. A microscopic examination of the urine, to include WBC, RBC, bacteria and casts will be performed if the urinalysis is abnormal.

7.2.7 Urine or Serum Pregnancy Test

A urine or serum pregnancy test will be obtained for all females of childbearing potential. Exempt female patients will include those who have undergone a bilateral oophorectomy or hysterectomy or who are menopausal (defined as absence of a menstrual cycle for at least 12 consecutive months).

7.2.8 Pharmacokinetic Assessments

Plasma samples will be collected to determine the levels of MM-398 and SN-38. Additional analytes which may impact the pharmacokinetics of MM-398 may also be measured from this sample. Directions for processing and shipping the PK plasma samples can be found in the study manual. The PK time points outlined in Table 13 below will be drawn during Cycles 1-3.

Table 13: Summary of PK Timepoints in Treatment and Follow-up Phases

Sample	Time-point (Cycles 1-3)	Window
1	Immediately prior to MM-398 infusion on Day 1	-5 mins
2	At the end of the MM-398 infusion	+5 mins
3	+2 hours after the completion of the MM-398 infusion	±30 mins
4	+ 48 hours after the completion of the MM-398 infusion	±24 hours
5	+168 hours/7 days after the completion of the MM-398 infusion	±24 hours
6	Immediately prior to MM-398 infusion on D15	-24 hours
7	30 day follow up visit	---

7.3 Tissue Collection

7.3.1 Fresh Tumor Biopsies

7.3.1.1 Pilot Phase Biopsies

Two biopsies will be collected on Day 4 of the ferumoxytol phase and two biopsies will be collected three days after the first dose of MM-398.

On Day 4 of the ferumoxytol phase, the lesion(s) selected for biopsy will be based on the results of the FMX-MRI obtained on Days 1, 2 and 4. The first core biopsy will be in the region of the tumor that shows the greatest signal change based on FMX-MRI and the second core biopsy will be taken from the region that shows the least signal change based on FMX-MRI.

On Cycle 1 Day 4 of the MM-398 Treatment phase, the lesion(s) selected for biopsy will be based on the results of the FMX-MRI obtained on Days 1, 2 and 4 of the ferumoxytol phase. The post-treatment biopsies will be collected from a previously non-biopsied lesion. The first core biopsy will be in the region of the tumor that shows the greatest signal change on either the T2* or T1 sequences, based on FMX-MRI. The second core biopsy will be taken from the region that shows the least signal change based on FMX-MRI, avoiding obvious areas of necrosis.

7.3.1.2 Expansion Phase Biopsies

A Post-treatment core biopsy must be collected at 72 h (+/- 1 day) after the C1D1 administration of MM-398. Any lesion that is amenable to a safe multi-pass core biopsy procedure may be selected. Expansion Phase patients in Cohort 3 with central nervous system (CNS) disease only are not required to undergo biopsy; however patients in Cohort 3 with non-CNS disease will be required to submit a biopsy sample, if a core biopsy can be safely obtained from a site of extracranial disease. Three passes should be obtained with the first two passes snap frozen and the third pass, if available, formalin fixed; See Laboratory Manual for details on processing and handling of the biopsy samples. Frozen samples will be used to measure tumor drug (CPT-11) and metabolite (SN-38) levels in order to further establish the mechanism of action of MM-398 and evaluate the relationship with tumor ferumoxytol levels as measured by FMX-MRI. Formalin fixed samples may be used to explore potential markers of sensitivity and resistance to irinotecan other pharmacodynamic markers related to activity of MM-398.

7.3.2 Archived Tumor Samples

Archived tumor blocks or unstained FFPE slides containing tumor tissue, prepared at the time of initial diagnosis and at the time of metastasis (if available) will be collected from each patient. Archived paraffin blocks may be used if available and will be returned to the site upon sectioning by sponsor or sponsor designated central lab. Samples will be used to explore potential markers

of sensitivity and resistance to irinotecan, including but not limited to the following: DNA damage repair pathways (e.g. Topo1, BRCA1/2, and SLFN11), growth factor pathways (IGF1 and EGFR family receptors and ligands), and factors involved in CPT-11 conversion to SN-38 (e.g. macrophage content and CES activity).

7.4 Ferumoxytol Magnetic Resonance Imaging

It is anticipated that the MRI parameters will need to be optimized in patients that are enrolled at the beginning of the study and/or in the Expansion Phase, in order to assess any correlations between FMX-MRI signal and TAMs, pharmacodynamic markers, or tumor response. A detailed FMX-MRI protocol is included in the study imaging manual, but briefly, each patient will be required to undergo their FMX-MRIs on the same scanner to reduce inter-scan variability. Each MRI study will be evaluated for image quality and signal characteristics of tumors and reference tissue on T1-, T2- and T2*- weighted sequences. Once a completed set of images from each patient has been received, the images will be loaded onto the viewing workstation for qualitative review and then sent to a quantitative lab for analysis.

During the Expansion Phase, multiple MR images will be collected on Day 1-Day 2 of the ferumoxytol period, at various time points depending on the scan group to which the patient is assigned. The body areas to be scanned will be determined by the location of the patient's disease; detailed instructions are described in the study imaging manual. All patients will have a baseline image acquired prior to the ferumoxytol infusion, and either a second successive image (baseline repeat; Scan Group 1) or a second image occurring 1-4 h after the end of ferumoxytol administration (Scan Groups 2 and 3). All patients will return on Day 2 for a 24 hour (16-24 h window) FMX-MRI using the same protocol and sequences as on Day 1. Patients enrolled into Scan Groups 1 and 2 will require one additional scan either at 24 h or 2 weeks, for a total of 4 scans. Patients will be assigned in an alternating fashion to Scan Groups 1 and 2 before enrollment into Scan Group 3 begins. See Table 14 below for additional details on scan groups and required time points.

Table 14: Summary of Expansion Phase MRI Scan Groups (Cohorts 1 and 2)

Scan Group	N[a]	Baseline	Baseline (repeat)	1-4 h	24 h (16-24 h)	24 h (repeat)	2 wk (+/- 1 Day) Baseline
1	5	X	X		X		X
2	5	X		X	X	X	
3	10	X		X	X		

[a] Enrollment into Scan Groups 1 and 2 may be increased at the discretion of the Sponsor, in the event that any of the images are not evaluable, or it is determined that more information is needed from the additional scan time points. In this case, enrollment into Scan Group 3 will be decreased by a corresponding number of patients.

Table 15: Expansion Phase Cohort 3 MRI Scan Time Points

Scan Group	N	Baseline	Baseline (repeat)	1-4 h	24 h (16-24 h)	24 h (repeat)	2 wk (+/- 1 Day) Baseline
4 (cohort 3)	10	X[a]		X[b]	X[a]		

[a] Patients with extra-cranial disease will have MRIs of two body areas at baseline and 24 h: one brain scan and one body scan (body scan will capture the majority of the patient's extra-cranial disease; see imaging manual for details)

[b] Brain scan only will be completed at this time point

8 Schedule of Assessments

8.1 Pilot Phase (Closed)

PILOT PHASE SCHEDULE OF ASSESSMENTS REMOVED (MM-398-01-01-02 Version 3.0). This portion of the trial has been completed and the schedule of assessments has been removed from this version of the protocol to reduce confusion during operation of Expansion phase.

8.2 Expansion Phase

Procedure	Screening Period	Ferumoxytol (FMX)Period		MM-398 Treatment Period							Follow Up Period
	-28d	Day 1	Day 2	Cycle 1[23], 2, and 3				Additional Cycles (every 1 month)[28]		Every 8w after 1st dose	+30d[22]
				D1	D3	D8	D15	D1	D15		
Informed consent	X[1]										
Medical history	X[1]										
Demographics	X[1]										
Physical exam	X[2]			X				X			X
Vital signs	X[2]	X[3]		X		X	X	X	X		X
ECOG PS	X[2]			X				X			X
CBC	X[2]			X		X	X	X	X		X
Serum chemistry[21]	X[2,16]			X		X	X	X[16]	X		X[16]
UGT1A1*28	X[1,17]										
Coagulation profile[21]	X[2]			X				X			X
Urinalysis	X[2]										X
Pregnancy test	X[2]										X
ECG	X[1,4]										X[4]
FMX-MRI		X[5]	X[6]				X[7]				
Ferumoxytol infusion		X[25]									
Tumor biopsy[8]					X[9]						
Archived tissue[10]	X										
Plasma for PK				X[11]	X[12]	X[13]	X[14]				X
Biomarker analysis[18,21]				X[14]				X			X
Concomitant meds	X[1]	X	X	X		X	X	X	X		X
MM-398 dosing[15]				X			X	X	X		
AE reporting	Continuous Monitoring										
Disease evaluation	X[1,24]									X[20]	X[19]

[1] Procedures to be completed within 28 days of ferumoxytol dose
[2] Procedures to be completed within 7 days of ferumoxytol dose
[3] Body weight to be collected within 7 days of ferumoxytol dose
[4] Two independent readings at least 1 minute apart
[5] Procedure completed at Cycle 2 only
[6] One reading prior to the start of the MM-398 infusion and one reading post infusion of MM-398 is required
[7] Two FMX-MRI collected as outlined in section 7.4 and Table 14 and Table 15
[8] One MRI at 24 h (16-24 hour window) except Scan Group 2, who will undergo 2 repeat scans at the 24 h timepoint
[9] For Scan Group 1 only, one MRI scan will be performed during Cycle 1 only (±1 day)

[10] Biopsy required for Cohorts 1 and 2, as well as Cohort 3 patients with extracranial disease that can be safely biopsied
[11] Post-Treatment Biopsy collected 72h post C1D1 MM-398 infusion
[12] Collection of archived tumor block or paraffin embedded slides, if available
[13] Samples collected at the following timepoints on C1D1 of the MM-398 Treatment Phase: just prior to the MM-398 infusion (-5 mins); at the end of the MM-398 infusion (+5 mins); +2 hours after the completion of the MM-398 infusion (±30 mins);
[14] Sample collected +48 hours after the completion of the MM-398 infusion (±24 hours)
[15] Sample collected +168 hours/7 days after the completion of the MM-398 infusion (±24 hours)
[16] Sample obtained just prior to dosing with MM-398 (-24 hour window)
[17] MM-398 administration should occur ±2 days from scheduled date of administration
[18] In addition to normal labs, iron levels will be measured at the screening visit, at the time of the first MM-398 dose of Cycle 2 (first additional cycle) and at the 30 Day Follow-up visit.
[19] Result not required prior to enrollment in the study., but patients positive for UGT1A1*28 Both the starting dose and dose modifications for toxicities will be the same for all patients regardless of UGT1A1*28 genotype, may have future doses reduced as described in section 6.1.6.3
[20] Blood will be collected for biomarker analyses
[21] Unless completed in the prior 6 weeks
[22] Disease evaluations should be done every 8 weeks (± 7 days) after 1st dose
[23] Visit for samples should be obtained ± 2 days from scheduled date of collection
[24] The 30-Day Follow-Up visit should occur 30 days (± 7 days) after last dose
[25] The Cycle 1 Day 1 visit should occur within 7 days of ferumoxytol infusion
[26] In addition to contrast-enhanced CT and/or MRI, ^{18}F-FDG PET/CT scan required at baseline only (patients with extracranial disease only)
[27] Administer while patient is in a reclined or semi-reclined position. Patients should be closely monitored for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during administration and for at least 30 minutes following the infusion as per the ferumoxytol label instructions. Ferumoxytol administration outlined in section 6.2.3.

9 Adverse Event Reporting

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, including abnormal laboratory findings, symptoms, or diseases temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Worsening of a medical condition for which the efficacy of the study drug is being evaluated will not be considered an adverse event.

9.1.2 Unexpected Adverse Event

An unexpected adverse event is one for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure.

9.1.3 Adverse Events of Special Interest

For this protocol the collection of Adverse Events of Special Interest (AESI) will be reported following serious adverse event reporting procedures as described below.

For this protocol, a specific AESI includes notification and collections of hypersensitivity reactions associated with the administration of ferumoxytol and will follow Serious Adverse Event notification procedures. Hypersensitivity reaction reports including anaphylaxis/anaphylactoid reactions should include individual signs and symptoms, time to onset, time to resolution and any intervention or medication given for the treatment thereof.

9.1.4 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Death due to disease progression is not considered an SAE and should not be recorded as such. Death due to disease progression should be recorded on the appropriate form in the electronic data capture system. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event term, as death is typically the outcome of the event, not the event itself.

9.2 Documenting Adverse Events

SAE reporting will begin on the date the patient provides informed consent to participate in the study. Treatment-emergent adverse event reporting will begin as of the administration of ferumoxytol. The Investigator should elicit information regarding the occurrence of adverse events through open-ended questioning of the patient, physical examination and review of laboratory results.

All adverse events, whether serious or not, will be recorded in the source documents and the adverse event page of the case report form (except as noted below). All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur after first administration of study drug through 30 days following the last dose of study drug, must be recorded. 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. However, new adverse events considered by the Investigator to be related to MM-398 or ferumoxytol, must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 30 days after the last dose of study drug.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

Information to be reported in the description of each adverse event includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- A determination of whether the event is serious or not
- Action taken: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; non-drug treatment required; hospitalization or prolongation of hospitalization required (complete serious adverse event page); diagnostic procedure performed; patient discontinued from the study (complete Final Visit Section of the case report form)
- Outcome: resolved without sequelae; resolved with sequelae; event resolving; event ongoing; patient died (notify the Sponsor immediately, and complete the Serious Adverse Event page and the Final Visit section of the case report form)

9.3 Reporting Serious Adverse Events

All fatal or life-threatening adverse events or adverse event of special interest (AESI) must be reported to the medical monitor immediately by telephone or e-mail. Within 24 hours of knowledge of the event, the Serious Adverse Event Form must be faxed to the appropriate contact whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known. Source documentation of

all examinations, diagnostic procedures, etc., which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of MM-398, even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor immediately (within 1 working day) using the AE and SAE forms. Overdose of MM-398 will be defined as ≥ 133% of planned dose.

All other serious adverse events must be reported to the appropriate contact within 24 hours of becoming aware of the event by phone, e-mail or fax. The Serious Adverse Event Form must also be faxed to the appropriate contact within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known.

The medical monitor shall be contacted as deemed necessary by the site. Current contact information shall be maintained at the site within the regulatory binder.

All SAEs will be evaluated by the medical monitor. If meeting the requirements for expedited reporting, the Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other Investigators involved in clinical trials with the study drug. The Investigator is responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB).

9.4 Determining the Severity and Relatedness of Adverse Events

9.4.1 Grading the Severity of an Adverse Event

Each adverse event will be graded according to the NCI CTCAE Version 4.02, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening or fatal which correspond to Grades 1, 2, 3, 4 and 5, respectively on the NCI CTCAE, with the following definitions:

- **Mild**: an event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate**: an event not resulting in disability or incapacity but which requires intervention;
- **Severe**: an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening**: an event in which the patient was at risk of death at the time of the event
- **Fatal**: an event that results in the death of the patient

9.4.2 Relatedness to Study Drug

The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study drug, according to the following guidelines:

The Investigator must attempt to determine if an adverse event is in some way related to the use of the study drug. This relationship should be described as follows:

- **Unlikely**: The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug
- **Possible**: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication
- **Probable**: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition which or the event cannot be the effect of a concomitant medication
- **Definite**: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug
- **Unknown**: Based on the evidence available, causality cannot be ascribed

9.4.3 Reporting and Follow-up of Pregnancy

Patients who become pregnant while on study must immediately discontinue MM-398, and the pregnancy must be immediately reported to the medical monitor. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the Sponsor.

The Investigator should inform the patient of the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event of a pregnancy occurring in the partner of a male patient participating in the study, the pregnant partner should be requested to report the pregnancy to the Sponsor. The partner should also be informed of the risks of continuing with the pregnancy, the possible effects on the fetus, and be followed until conclusion of the pregnancy.

10 Data Management and Statistical Analysis

10.1 Case Report Forms

All data for the patients recruited for the trial will be entered onto electronic case report forms (eCRFs) via an Electronic Data Capture system provided by the Sponsor. The following information for the patients who screen-failed will be entered into the database: screening visit date, informed consent form, demographics, eligibility, adverse events, concomitant medication and procedures, and overall study termination. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

10.2 Data Quality Assurance

Electronic CRFs will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the Investigator or the study site staff to make appropriate corrections, and the corrected eCRF will

again be reviewed for completeness and consistency. Any discrepancies will be noted in the CRF system by means of electronic data queries. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines.

10.3 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. The SAP may modify the analysis outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

No formal hypothesis testing will be performed in the Pilot or Expansion Phases of this study. Descriptive statistics will be calculated to summarize categorical and continuous parameters. Parameters will be reported by cohort and overall, according to Pilot and Expansion Phase. When appropriate, the Pilot and Expansion study phases may be pooled. At the minimum, categorical parameters will be summarized by frequency and percentage, while continuous parameters will be summarized by n, mean, standard deviation, median, minimum and maximum. Time-to-event parameters will be graphically displayed using Kaplan-Meier estimates. Median event times and 2-sided 95% confidence intervals will be reported on the graphs. Two-sided 95% confidence intervals (CI) may be displayed for some other parameters. All analyses will be performed in SASv9.2 or higher. No interim analysis will be performed.

A cycle is defined as 28 days in length starting with Cycle 1 Day 1 as the first dose date of MM-398. Data will be analyzed according to the cycle in which it actually occurred.

10.4 Study Populations

The Pilot and Expansion Phases will be analyzed according to safety and efficacy parameters. Similar constraints will be applied according to study phase.

- The safety population will include all patients receiving at least one dose of MM-398 or ferumoxytol. Depending upon patients receiving MM-398 and not ferumoxytol and vice versa, the safety population may be expanded in order to not dilute any adverse event rate
- The efficacy evaluable population includes all patients receiving at least one dose of MM-398.
- The pharmacodynamic evaluable population includes all efficacy evaluable patients with the following: a) pre-treatment FMX-MRI scan(s) and b) radiological scans at 8 weeks.
- The pharmacokinetic population includes patients receiving at least one dose of MM-398 and blood samples adequately collected at the predefined points.

10.5 Disposition and Baseline Characteristics

Study populations (enrolled, safety, efficacy evaluable, pharmacodynamics evaluable, PK) will be summarized and displayed as frequencies. Disposition of patients will be tabulated as those discontinued MM-398 and reason for discontinuation. Demographic and baseline characteristics will be summarized. Medical history and prior medications will be tabulated as well.

10.6 Efficacy Analysis

Tumor evaluation will be measured according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (Cohort 1 and 2, and non-CNS disease for Cohort 3) or modified RECIST

as defined in section 7.1.6.1 (CNS disease; Cohort 3 only). Best Overall Response (BOR) is defined as the best response as recorded from the start of MM-398 until disease progression.

Objective Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Exact 95% confidence intervals based on the binomial distribution will be reported.

Clinical benefit rate is defined as the proportion of patients with a BOR characterized as a CR, PR, or Stable Disease (SD) ≥ 24 weeks. Proportion of patients relative to the total number of evaluable patients will be reported with exact 95% confidence intervals based on the binomial distribution.

Duration of Response (DR) is defined as the time from first documentation of response (CR or PR whichever occurs first) to the date of disease progression or to death due to any cause, whichever occurs first.

Progression-free survival (PFS) is defined as the time from first dose of MM-398 to the date of radiologic disease progression by RECIST per Investigator or death due to any cause, whichever occurs first. Rules for declaring PFS events versus censors will be described in the SAP.

A waterfall plot will be used to display BOR with maximum percent decrease in target lesion and FMX uptake value at 24 hours.

FMX uptake (ug/mL and/or %ID/kg) will be summarized as a continuous parameter. Absolute and change from baseline will be summarized. The number of target lesions decreasing, staying the same, increasing relative to FMX uptake with various thresholds will be summarized by frequency and percent according to cycle. Box and whisker plots will be displayed for FMX uptake by time point. The relationship between FMX uptake at 1-4 hours and/or 24 hours with tumor response will be evaluated using various parameters and methods. Relationships may be explored as appropriate. Additionally, informal Fisher's exact test will be used to investigate dichotomous FMX cutpoints as related to ORR. Other graphical procedures may be implemented to explore the relationship between FMX and efficacy response.

10.7 Safety Analysis

Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by Sponsor's current MedDRA version. Adverse event coding will be performed to the lowest level term. Frequency and percent summaries will be presented for treatment-emergent adverse events (TEAE) defined as adverse events that occur or worsen in severity following the first dose of MM-398 or ferumoxytol, serious adverse events (SAE), TEAE-related to MM-398 or ferumoxytol and TEAE grade ≥ 3, and discontinuation due to TEAE. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

Toxicity grading will be assigned according to NCI CTCAE when possible. Absolute laboratory values will be summarized by visit. Maximum and minimum change from baseline laboratory data will be summarized. Baseline will be the last measurement taken prior to the first study drug administration of MM-398. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) will be assessed. Shift to most severe toxicity grade will be summarized.

Vital signs will be tabulated for the change from baseline by timepoint. Additional analyses may be performed as described in detail within the SAP.

10.8 Biomarker Subgroup Analysis

Biomarker subgroup analyses will be analyzed for efficacy parameters (ORR, percent change in target lesion size, and PFS or as appropriate). Graphical displays will be performed when appropriate.

10.9 Pharmacodynamic Marker Analysis

Spearman pairwise correlations will be computed between the following measurements obtained from the Pilot Phase of the study:

- FMX-MRI levels
- Tumor associated macrophage levels
- Tumor irinotecan levels
- Tumor SN-38 levels

Graphical and regression methods will be used to explore potential relationships among correlated measurements. In addition, relationships between pharmacodynamics markers and efficacy response will be evaluated in an exploratory manner in both the Pilot Phase and Expansion phases of the study.

10.10 Pharmacodynamic Analysis

Pharmacokinetic parameters will be derived from the blood PK samples and will be analyzed using descriptive statistics, including the median, mean and 95% confidence intervals around parameter estimates by dose level. All PK parameters will include Cmax, Tmax, AUC (area under the concentration curve), clearance, volume of distribution at steady state (Vdss), and the terminal elimination half-life. Estimation of the pharmacokinetic parameters will be performed using standard non-compartmental methods.

10.11 Sample Size and Statistical Hypothesis

No formal hypothesis testing will be performed for this study, therefore the Pilot and Expansion Phases are not appropriately powered to detect statistical differences. The Pilot Phase will enroll between 12 and 20 patients with various indications, while the Expansion Phase will enroll approximately 30 metastatic breast cancer patients across 3 cohorts.

For the Pilot Phase, Table 16 provides some probabilities of observing a particular adverse event.

Table 16: Probability to Detect an Adverse Event with N=12 Patients

True Event Rate	Probability to Observe at Least 1 Event	Probability to Observe More than 1 Event
0.05	0.46	0.12
0.10	0.72	0.34
0.15	0.86	0.56
0.20	0.93	0.73
0.25	0.97	0.84

The Expansion Phase ORR is estimated to be around 29% with a 95% confidence interval (14.6-46.3) [36]. Other studies showed similar response rates ranges ranging from 5-32% [33].

Hypothesizing a true ORR of 30%, the probability of at least 14 responses of 30 evaluable patients would be 0.04. The probability of at least 13 responses would be 0.084.

11 Extension Phase

Following fulfillment of analysis requirements, the Sponsor may elect to reduce follow-up to minimally required safety collection. Patients will be followed per standard of care to assess for safety and the required visits in the schedule of assessments are no longer applicable. All AEs meeting SAE reporting requirements or AESI for which the investigator feels are of greater incidence or severity than presented in the IB must be submitted as per section 9.3.

12 Study Administration

12.1 Pre-study Documentation

Prior to initiating the trial, the Investigator will provide to the Sponsor or designee the following documents:

- A signed FDA Form 1572
- A current (i.e. updated no more than 24 months prior) curriculum vitae for the Principal Investigator and each sub-Investigator listed on the FDA Form 1572
- A copy of the current medical license for the Investigator and each sub-Investigator
- A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g., advertisements)
- A copy of the IRB-approved informed consent document
- The current IRB membership list for the reviewing IRB, or the multiple project assurance number from the Federal Wide Assurance program (www.ohrp.osophs.dhhs.gov).
- A signed Investigator Protocol Agreement
- A completed financial disclosure form for the Investigator and all sub-Investigators
- A current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory

12.2 Source Documents

The Investigator will maintain records separate from the eCRFs in the forms of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The Investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms when the Sponsor's monitor visits the investigational site. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. All information obtained from source documents will be kept in strict confidentiality. Source data sent as supporting documentation for serious adverse events will be de-identified to preserve confidentiality.

12.3 Trial Ethics

The study will be performed according to the principles of the Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm), the International Conference on Harmonization Guidance

on Good Clinical Practice and the requirements of the US FDA regarding the conduct of human clinical trials.

12.4 Patient Informed Consent

No study related procedures will be performed until a patient or a patient's legal representative has given written informed consent. The Sponsor will provide to the Investigator a sample informed consent document that includes all the requirements for informed consent according the ICH GCP, U.S. FDA guidelines (21 CFR 50) and/or local regulatory guidelines. However, it is up to the Investigator to provide a final informed consent that may include additional elements required by the Investigator's institution. The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the trial and who signs the informed consent will be given a copy of the signed, dated and witnessed document (the witness signature is only required for cases that fit the criteria for needing a witnessed signature). The provision of informed consent will be documented in the medical record.

12.5 Investigational Review Board

The trial will not be initiated until there is approval of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial by the local IRB. The IRB should be duly constituted according to local regulatory requirements. Approval must be in the form of a letter signed by the Chairperson or the Chairperson's designee, must be on official stationary and must include the protocol by name and/or by designated number. If an Investigator is a member of the IRB, then the approval letter must stipulate that the Investigator did not participate in the final vote, although the Investigator may participate in the discussion of the trial. The Investigator will also inform the IRB of any SAEs that the Sponsor reports to regulatory authorities, will report on the progress of the trial at least yearly (or more frequently if required by local regulation or guidance) and will provide to the IRB a final summary of the results of the trial at the conclusion of the trial.

12.6 Monitoring

A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the trial. The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The Investigator will allow the Sponsor or designee access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor.

In addition to the above, representatives of the FDA may review the conduct or results of the study at the investigational site. The Investigator must promptly inform the Sponsor of any audit

requests by health authorities, and will provide the Sponsor with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personally identifiable health information may be required for each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

12.7 Confidentiality

It is the responsibility of the Investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted to the Sponsor must never contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRF's and any other material submitted to the Sponsor. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

12.8 Confidentiality of Biomarker Samples

Blood samples collected as part of the biomarker analysis will be identified only by a number assigned to the patient at the study site; this number will be used in lieu of the patient's name in order to protect the patient's identity. The samples will be stored at a facility designated by the Sponsor. Other than the patient's unique identifying number, no additional patient information will be stored with these samples. Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens will be stored for a maximum of 5 years after study completion. At that time, any remaining samples will be destroyed. At the time of informed consent, patients will be able to refuse long-term storage of these remaining samples. If long-term storage is refused, any remaining samples will be destroyed following the initial specified analyses. Similarly, patients may withdraw approval at any time by submitting a written request to their study site Investigator. Upon receipt of this withdraw of consent, no further analyses will be completed and the patient's remaining samples will be destroyed, however, data already collected will not be removed from the study dataset.

Any samples that a patient consents to long-term storage may be used by the Sponsor for future research. The results from these exploratory analyses may not necessarily be shared with the Investigators or the participating patients.

12.9 Protocol Amendments

The protocol will only be amended with the consent of the Sponsor and the IRB. Changes to the protocol must be in the form of a written amendment; changes other than those of a simple administrative nature (e.g., a new telephone number for a medical monitor) must be submitted by the Investigator to their IRB and such amendments will only be implemented after approval of the requisite IRB. All amendments will also be submitted to the FDA by the Sponsor.

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the Investigator immediately. The Investigator must then immediately inform the local IRB or EC and the Sponsor will immediately notify local regulatory authorities.

12.10 Publication

As the Study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this Study at all sites, the Investigator shall have the right to publish or present independently the results of this patient to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least forty-five (45) days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the Collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor or its designee has the right at any time to publish the results of the Study.

12.11 Records Retention

The Investigator will retain the records of the clinical trial (including, but not necessarily limited to, CRFs, source documents, informed consent forms, drug accountability records, IRB correspondence, Sponsor correspondence, etc.) for 2 years following the date that the last marketing application for the study drug is approved, or if no marketing application is filed, or if such an application is not approved, for 2 years after the formal discontinuation of clinical development of the study drug. The Sponsor or designee will notify Investigators when retention of study records is no longer required. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary.

Study records must be retained as per the GCP guidelines and local regulatory requirements, including, but not limited to, case report forms, signed informed consents, correspondence with the IRB/EC, study drug dispensing and inventory records, source documents (clinic charts, medical records, laboratory results, radiographic reports) and screening/enrollment logs.

Should the Investigator relocate or retire the responsibility for maintaining the study records may be transferred to another Investigator. The Sponsor must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the study records.

12.12 Study Termination

The Sponsor reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment

- Safety concerns
- Drug supply or manufacturing issues
- The Sponsor's decision to modify or discontinue the development MM-398
- A request to discontinue the study by the FDA and/or local regulatory authorities.

The Sponsor will promptly inform all Investigators and the FDA and/or local regulatory authorities if the study is suspended or terminated for any reason. The Investigator will promptly notify their IRB if the study is suspended or terminated.

13 Investigator Signature Page

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I will identify study personnel conducting study specific procedures and appropriately document their training and/or delegated responsibilities. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the patients in the study.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

_____ _____

Signature of Investigator Date

_____

Print Name of Investigator

_____ _____

On behalf of the Sponsor Date

PPD
PP Oncology and Endocrinology
Global Drug Development, R&D
IPSEN

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Protocol Amendment Summary

A Pilot Study in Patients Treated with MM-398 to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages

Summary of changes from Protocol version 1.0 dated 26 Aug 2012 to version 2.0 dated 2 May 2013

Sponsor:

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EudraCT Number: 2011-004687-30

Overview

The overall changes and rationale for the changes incorporated in this protocol are as follows:

- **Section 2. Background**
  This section was updated to include details on the disease indications that were included for the protocol and to provide a background and rationale for these additional indications.

- **Section 2.1.4. Clinical Experience**
  This section was updated to clarify the UGT1A1 allele that is analyzed.

- **Section 2.2.3. Interaction of ferumoxytol and MM-398**
  The number of patients to be enrolled was clarified to provide a maximum number. Between 12 and 20 patients will be enrolled in this study.
  This change has been made throughout the protocol, where applicable.

- **Section 3. Objectives**
  Sections 3.1 Primary Objectives, 3.2 Secondary Objectives, and 3.3 Exploratory Objectives were updated per changes to the disease indications added. These changes have been made throughout the protocol, where applicable.

- **Section 4. Study Design**
  This section was updated with the added disease indications, as above. Also, a cap to the number of patients with ER/PR positive breast cancer was introduced. The rationale for the selection of added disease indications was included.

- **Section 4.1. Enrollment and Treatment**
  The number of patients to be enrolled was clarified to provide a maximum number, as above.

- **Section 5.1. Inclusion Criteria**
  - The inclusion criterion a) was updated with the added disease indications.
  - The inclusion criterion b) was updated to provide clarification on the required size of the lesion(s) for the biopsies.

- **Section 6.1.6. Dose Reduction Due to Toxicity**
  This section was updated to clarify the CTCAE version used in this study.

- **Section 7.1.6. Disease Evaluation**
  This section was updated to remove the language regarding the extent of disease assessment. Per RECIST guidelines, no extent of disease assessment is required for disease evaluation.

- **Section 7.2.2 Serum Chemistry**
  Iron levels measurements were added at the 30 Day Follow-up visit.

- **Section 7.2.3. Serum Biomarkers**
  This section was updated to correct the list of samples to be collected. Also, the section heading was updated to reflect these corrections.

- **Section 7.2.6. Urinalysis**
  This section was updated to correct an error. Presence of blood rather than hemoglobin level will be analyzed in the urinalysis.

- **Section 7.2.8. Pharmacokinetic Assessments**
  This section was updated to correct several errors.
  - Plasma rather than serum samples will be collected for PK analyses.
  - Table 12 was corrected to include a PK timepoint that had been missed in error, but was present in the schedule of assessments (section 8).
  - Tables 11 and 12 were updated to add window periods for sample collection.

- **Section 7.3.1. Fresh Tumor Biopsies**
  This section was updated to clarify the MRI images to be used for the selection of lesions to biopsy.

- **Section 7.4. Ferumoxytol Magnetic Resonance Imaging**
  This section was updated to clarify the MRI collection schedule and process.

- **Section 8. Schedule of Assessments**
  - The cycle break-down in weeks was changed to days to clarify the due dates for all assessments.
  - The screening procedures must be completed within 28 or 7 days of ferumoxytol dose, and not from the first dose of MM-398.
  - The body weight for ferumoxytol dose on Day 1 can be collected within 7 days of dosing.
  - Two independent ECG readings will be performed at the 30 Day Follow-up visit.
  - The 2 independent ECG readings at screening and follow-up are to be completed at least 1 minute apart and no longer 5 minutes apart.
  - The PK samples to collect were changed from serum to plasma to reflect the clarification made in section 7.2.8.
  - The Fe-MRI collection schedule on ferumoxytol phase Day 1 was updated in the footnotes to reflect the clarification made in section 7.4.
  - Iron levels will be measured at the 30 Day Follow-up visit.

  - Windows for all samples collection, disease assessment, 30 Day Follow-up visit were included.
  - Footnotes were updated to provide clarifications regarding the assessments outlined in the table.

- **Section 9.2. Documenting Adverse Event**
  This section was updated to clarify the starting time for treatment-emergent adverse event reporting.

- **Section 10.1. Case Report Forms**
  This section was updated to include what information will be collected in the database for screen-failed patients.

- **Section 10.3. Sample Size**
  The number of patients to be enrolled was clarified to provide a maximum number of patients to be enrolled, as above.

- **Section 12. References**
  - Errors in references were corrected.
  - Included references for data added in section 2.

Revised Protocol Sections

Note: All deletions have been identified by ~~strikethroughs.~~
All additions have been identified by underlining.
Administrative changes, changes to correct grammatical, spelling or formatting errors, and changes in numbering of the sections, tables or figures, are not included in this section.
All changes in the protocol were added to the study synopsis (section 1).

Section 2. Background

……...

To maximize the information from this study, patients that are most likely to achieve the objectives of the study will be enrolled. Although the first three patients enrolled in the study can have any solid tumor, subsequent patients will be limited to ~~those with colorectal~~ a subset of indications. Selection of these indications is based on the expected higher levels of tumor-associated macrophages, the potential sensitivity to irinotecan based on clinical experience and/or the presence of the pro-drug converting carboxyl esterase enzymes (CES) and the amenability to imaging and biopsy collection. These indications include colorectal cancer (CRC), non-small cell lung cancer (NSCLC) ~~or~~, triple negative breast cancer (TNBC). ~~These three tumor types were selected based on:~~, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma and head and neck cancer. No more than three patients with ER/PR positive breast cancer can be enrolled in the study and similar restrictions may be placed on other tumor types to ensure a heterogeneous population at study end.

~~- Probable high levels of macrophages~~
~~- Potential sensitivity to irinotecan based on the presence of the converting carboxylesterase enzyme (CES) and/or clinical experience~~
~~- Amenability to imaging and biopsy collection~~

Merrimack Pharmaceuticals' tumor microarray analysis of patient samples showed that both colorectal CRC and NSCLC have a significant subset with higher levels of the CD68 marker for tumor associated macrophages. ~~In addition,~~ This is in agreement with published findings reviewed by Heusinkveld and van der Burg (2011) [24]. This review also provides supportive information on the presence of tumor-associated macrophages in other indications, including ovarian, gastric and pancreatic cancers. Head and neck cancer has been shown to achieve high deposition of pegylated liposomes in an imaging study by Harrington et al. (2001) [25] and contains many immune cells, including phagocytic dendritic cells and macrophages (reviewed in [26, 27]). In-house profiling of human primary xenografts showed high CES enzyme activity (measured by tumors ability to convert irinotecan to SN38) in CRC and NSCLC patient tumor samples.

……...

Similarly, Nogami et al (2012) reported that in a phase II study the combination of irinotecan and amrubicin was effective in patients with relapsed NSCLC [5]. Combinations of cetuximab with irinotecan have shown promising responses particularly in TNBC [6]. ~~—~~ and more recently also in

gastro-oesophageal cancer [28, 29, 30]. Finally, topoisomerase I inhibitors such as topotecan and irinotecan provide very effective and tolerable treatment options for recurrent ovarian cancer [31].

Section 2.1.4. MM-398 Clinical Experience

……

TABLE 2: SUMMARY OF ONGOING STUDIES WITH MM-398

Study	UCSF 8603		PIST-CRC-01	PEPCOL	NAPOLI-1
Tumor Type	Glioma		Colorectal	Colorectal	Pancreas
Phase	1		1	2	3
Study design	Open label, dose escalation		Open label, dose escalation	Comparison of MM-398 + 5FU/LV + avastin versus FOLFIRI + avastin	Randomized comparison of MM-398 and MM-398+ 5-FU/LV *vs* a common control of 5-FU/LV
Dosing Frequency	Q3W		Q2W	Q2W	Q3W (monotherapy) Q2W (combination)
Dose Level (mg/m²)	HTZ[1] 60 (n = 3) 90 (n = 5)	WT[2] 120 (n = 6) 180 (n = 4) 240 (n = 3)	80 (n = 6) 90 (n = 6) 100 (n = 6)	80	120 (monotherapy) 80 (combination)
Combination	No		No	5FU/LV	5FU/LV
Combination dose	---		---	2400/400 mg/m² (5FU/LV) 5 mg/kg (avastin)	2000/200 mg/m²
Current status	MTD identified for HTZ; escalation ongoing for WT		Enrollment completed in final cohort	Enrollment ongoing	Enrollment ongoing

[1]Heterozygous for UGT1A1*28 [2]Wildtype for UGT1A1*28

Section 2.2.3. Interaction of ferumoxytol and MM-398

……

In this pilot study, we propose to use Fe-MRI imaging in ~~12~~up to 20 patients being treated with MM-398 to both determine the imaging parameters that could be applied to future clinical trials and to better define the appropriate strategy for incorporating ferumoxytol in TAM imaging for MM-398 studies.

……

Section 3. Study Objectives

Section 3.1. Study Objectives

In patients with ~~CRC, NSCLC, TNBC or other solid tumors~~NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma or head and neck cancer, who are undergoing therapy with MM-398:

- To evaluate the feasibility of delayed ferumoxytol MRI (Fe MRI) to identify tumor associated macrophages (TAMs)
- To measure tumor levels of irinotecan and SN-38

Section 3.2. Secondary Objectives

In patients with ~~CRC, NSCLC, TNBC or other solid tumors~~NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma or head and neck cancer, who are undergoing therapy with MM-398:

- To estimate the correlations between Fe-MRI, TAM levels, and tumor levels of irinotecan and SN38 with administration of MM-398
- To determine the value of Fe-MRI in directing tissue biopsy
- To characterize the safety profile of MM-398 in the presence of ferumoxytol
- To assess tumor response
- To characterize the PK of MM-398

Section 3.3. Exploratory Objectives

In patients with ~~CRC, NSCLC, TNBC or other solid tumors~~NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma or head and neck cancer, who are undergoing therapy with MM-398:

- To estimate the correlations between potential pharmacodynamic markers (Fe-MRI, TAM, tumor irinotecan, tumor SN38 levels) and safety
- To estimate the correlations between potential pharmacodynamic markers (Fe-MRI, TAM, tumor irinotecan, tumor SN38 levels) and tumor response
- To characterize each tumor biopsy to permit multivariate comparative analyses between tumor characteristics, Fe-MRI signal and drug metabolite levels

Section 4. Study Design

This study will enroll ~~at least 12 patients with NSCLC, CRC, TNBC or other solid tumors. After the first~~ approximately 12 patients, up to 20 in total. The first three patients that are enrolled can have any solid tumor type; however subsequent patients must have NSCLC, CRC, TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, gastro-oesophageal junction adenocarcinoma or head and neck cancer. No more than three patients~~, only patients with NSCLC, CRC or TNBC will be enrolled.~~ with ER/PR positive breast cancer can be enrolled in the study and similar restrictions may be placed on other tumor types to ensure a heterogeneous population at study end.

These indications were selected based on data suggesting that these tumor types have high levels of CD68 (tumor associated macrophages) and carboxylesterase enzyme (CES) activity~~,~~ or high levels of deposition, any of which may correlate to MM-398 response.

There are four stages to this study:

……

- MM-398 Treatment Phase (Day 5/C1D1 – progression of disease): patients receive an MM-398 dose of 80 mg/m^2 every 2 weeks and undergo biopsies and other required assessments

……

Section 4.1. Enrollment and Treatment

~~At least~~Between 12 and 20 patients will be enrolled in this study.

……

Section 5.1. Inclusion Criteria

In order for inclusion into the study, patients must have/be:

a) For the first three patients enrolled, pathologically confirmed solid tumors that have recurred or progressed following standard therapy, or that have not responded to standard therapy, or for which there is no standard therapy, or who are not candidates for standard therapy. For patients subsequently enrolled, pathologically confirmed NSCLC, CRC, ~~NSCLC or~~ TNBC, ER/PR positive breast cancer, pancreatic cancer, ovarian cancer, gastric cancer, GEJ adenocarcinoma or head and neck cancer that has recurred or progressed following standard therapy or that have not responded to standard therapy, or for which there is no standard therapy, or who are not candidates for standard therapy.
b) Documented metastatic disease with 2 lesions measuring at least 2 cm in diameter, and amenable to multiple pass percutaneous biopsies. In rare circumstances, only a single metastatic lesion may be amenable to percutaneous biopsy. A subject may still be a candidate for this trial provided that the single target lesion is substantial enough in size to allow for multiple pass biopsies on multiple days and, in the opinion of the interventional radiologist, multiple passes from the Pre MM398 biopsy will not overlap or interfere with the planned Post MM 398 biopsy.

……

Section 6.1.6. Dose Reduction Due to Toxicity

The toxicity of each cycle must be recorded prior to the administration of a subsequent cycle and graded according to the NCI CTCAE (Version 4.02).

……

Section 7.1.6. Disease Evaluation

Tumor response will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, to establish disease progression by computed tomography or MRI. In addition, other radiographic or scintigraphic procedures (such as radionuclide bone scans), as deemed appropriate by the Investigator, will be performed to assess sites of neoplastic involvement. The same

method of assessment must be used throughout the study. Investigators should select target and non-target lesions in accordance with RECIST v1.1 guidelines. Follow up measurements and overall response should also be in accordance with these guidelines.

~~The extent of disease assessment should be completed until it has been determined the patient has progressive disease (in accordance with RECIST v1.1). In the event the patient discontinues study treatment for reasons other than disease progression, an extent of disease assessment should be completed as soon as possible relative to the date of study termination to ensure disease progression is not present and to assess overall disease status. In such patients, this assessment should occur no later than the date of the 30 day follow up visit.~~

Section 7.2.2. Serum Chemistry

……

Iron levels (ferritin, iron and transferrin saturation) will be measured at the screening visit, ~~and~~ at the time of the first MM-398 dose of Cycle 2 (first additional cycle) ~~only~~ and at the 30 Day Follow-up visit.

Section 7.2.3. ~~Serum Biomarkers~~ Biomarker Samples

~~Serum~~Whole blood, plasma and urine will be collected to potentially identify factors that may correlate with tumor response and resistance to MM-398.

……

Section 7.2.6. Urinalysis

A urinalysis will include descriptions of color and clarity; pH; specific gravity; and analyses of ~~hemoglobin~~blood, glucose, ketones and total protein.

……

Section 7.2.8. Pharmacokinetic Assessments

~~Serum~~Plasma samples will be collected to determine the levels of MM-398 and SN-38.

……

TABLE 11 SUMMARY OF PK TIMEPOINTS IN FERUMOXYTOL PHASE

Sample	Time-point	Window
1	Immediately prior to ferumoxytol infusion	~~-~~5 mins
2	At the end of the ferumoxytol infusion	~~±~~+5 mins
3	+2 hours after the completion of the ferumoxytol infusion	±30 mins

4	+24 hours after the completion of the ferumoxytol infusion	± 1 hour
5	Immediately prior to Day 4 biopsy	-~~-~~30 mins

TABLE 12 SUMMARY OF PK TIMEPOINTS IN TREATMENT AND FOLLOW-UP PHASES

Sample	Time-point	Window
1	Immediately prior to MM-398 infusion on Day 1	-~~-~~5 mins
2	At the end of the MM-398 infusion	~~±~~+5 mins
3	+2 hours after the completion of the MM-398 infusion	±30 mins
4	Immediately prior to the Day ~~3~~4 post treatment biopsy	-~~-~~30 mins
5	+168 hours/7 days after the completion of the MM-398 infusion	±24 hours
6	Immediately prior to MM-398 infusion on C1D15	-24 hours
~~6~~7	30 day follow up visit	---

Section 7.3.1. Fresh Tumor Biopsies

……

On Day 4 of the ferumoxytol phase, the lesion(s) selected for biopsy will be based on the results of the Fe-MRI obtained on Days 1, 2 and 4.

……

On Cycle 1 Day ~~3~~4 of the MM-398 Treatment phase, the lesion(s) selected for biopsy will be based on the results of the Fe-MRI obtained on Days 1, 2 and 4 of the ferumoxytol phase.

……

Section 7.4. Ferumoxytol Magnetic Resonance Imaging

……

Two MRI images will be collected on Day 1 of the ferumoxytol phase. The first image will be acquired prior to the ferumoxytol infusion, and the second one, immediately after the end of ferumoxytol administration. The subjects will return on Day 2 and Day 4 for delayed Fe-MRIs using the same protocol and sequences as on Day 1.

Section 8. Schedule of Assessments

Procedure	Screening Phase	Ferumoxytol Phase			MM-398 Treatment Phase										Follow Up Phase
					Cycle 1					Additional Cycles				Every 8w after 1st dose	
	-28d	Day 1	Day 2	Day 4	~~Wk~~ D1	~~Wk~~ 2D4	~~Wk~~ 3D8	~~Wk~~ 4D15	D22	~~Wk~~ D1	~~Wk~~ 2D8	~~Wk~~ 3D15	~~Wk~~ 4D22		+30d[25]
Informed consent	X[1]														
Medical history	X[1]														
Demographics	X[1]														
Physical exam	X[2]				X					X					X
Vital signs	X[2]	X[3]			X	~~X~~	X	X		X		X			X
ECOG PS	X[2]				X					X					X
CBC[24]	X[2]				X	~~X~~	X	X		X		X			X
Serum chemistry[24]	X[2,14],[2,18]				X	~~X~~	X	X		X[14,18]		X			X[18]
UGT1A1*28	X[2,15],[2,19]														
Coagulation profile[24]	X[2]				X					X					X
Urinalysis[24]	X[2]														X
Pregnancy test	X[2]														X
ECG	X[1,3],[1,4]									X[4,5],[4,6]					X[4]
Fe-MRI		X[17]	X	X											
Ferumoxytol infusion		X													
Percutaneous biopsy				X[13],[16]	X[11,13]	X[14,16]									
Archived slides[10],[22]	X														
~~Serum~~Plasma for PK		X[6],[7]	X[7],[8]	X[8],[9]	X[9],[10]	X[10],[11]	X[10],[12]	X[13]							X
Biomarker analysis[16],[20],[24]					X		~~X~~	X		X		X			X
Concomitant meds	X[1]	X	X	X	X	~~X~~	X	X		X		X			X
MM-398 dosing[12],[15]					X		~~X~~	X		X		X			
AE reporting		X	X	X	X	~~X~~	X	X		X		X			X
Disease evaluation	X[1]													X[23]	X[17],[21]

Footnotes:

1. Procedures to be completed within 28 days of ~~first~~ferumoxytol dose ~~of MM-398~~
2. Procedures to be completed within 7 days of ~~first~~ferumoxytol dose ~~of MM-398~~
3. Body weight to be collected within 7 days of ferumoxytol dose
4. ~~3.~~ Two independent readings at least ~~5 minutes~~1 minute apart ~~prior to the start of MM-398 infusion~~
5. ~~4.~~ One reading prior to the start of the MM-398 infusion and one reading post infusion of MM-398 is required
6. ~~5.~~ Procedure completed every 2 cycles for each additional cycle
7. ~~6.~~ Samples collected at the following timepoints: immediately prior to ferumoxytol infusion (-5 min); at the end of the ferumoxytol infusion (±5 mins) and +2 hours after the completion of the ferumoxytol infusion (±30 mins)
8. ~~7.~~ Sample collected +24 hours after the completion of the ferumoxytol infusion (±2 hours)
9. ~~8.~~ Sample collected immediately prior to ferumoxytol Day 4 biopsy (-30 mins)
10. ~~9.~~ Samples collected at the following timepoints ~~in~~on C1D1 of the MM-398 Treatment Phase: just prior to the MM-398 infusion (~~±~~-5 mins); at the end of the MM-398 infusion (±5 mins); +2 hours after the completion of the MM-398 infusion (±30 mins);
11. Sample collected immediately prior to the Day ~~3~~4 post treatment biopsy ~~and~~(-30 mins)
12. Sample collected +168 hours/7 days after the completion of the MM-398 infusion (±24 hours)
13. ~~10.~~ Sample obtained just prior to dosing with MM-398 (±24 hours)
14. ~~11.~~ Biopsy collected +72 hours/3 days (± 3 hours) after the completion of the MM-398 infusion
15. ~~12.~~ MM-398 administration should occur ±2 days from scheduled date of administration
16. ~~13.~~ Two biopsies collected as outlined in Section 7.3

17. Two Fe-MRI collected as outlined in Section 7.4
18. ~~14.~~ In addition to normal labs, iron levels will be measured at screening visit ~~and~~, at the time of the first MM-398 dose of Cycle 2 (first additional cycle) ~~only~~ and at the 30 Day Follow-up visit.
19. ~~15.~~ Result not required prior to enrollment in the study, but patients positive for UGT1A1*28 may have future doses reduced as described in Section 6.1.6.3
20. ~~16.~~ Urine and blood will be collected for biomarker analyses
21. ~~17.~~ Unless completed in the prior 6 weeks
~~18. Final PK draw from week 1 visit (i.e. +168 hours/7 days after the completion of the MM-398 infusion)~~
22. ~~19.~~ Collection of archived tumor block or paraffin embedded slides is optional
23. Disease evaluations should be done every 8 weeks (± 7 days) after 1st dose
24. Samples should be obtained ± 2 days from scheduled date of collection
25. The 30-Day Follow-Up visit should occur 30 days (± 7 days) after last dose

Section 9.2. Documenting Adverse Event

……

Treatment-emergent adverse event reporting will begin as of the ~~first dose~~ administration of ferumoxytol.

……

Section 10.1. Case Report Forms

……

The ~~data~~following information for the patients who screen-failed will ~~not~~ be entered into the database: screening visit date, informed consent form, demographics, eligibility, adverse events, concomitant medication and procedures, and overall study termination.

……

Section 10.3. Sample Size

~~Approximately~~ Between 12 and 20 patients will be enrolled in this study.

……

Section 12. References

[1] Weinstein JS, Varallyay CG, Dosa E, et al. Superparamagnetic iron oxide nanoparticles: diagnostic magnetic resonance imaging and potential therapeutic applications in neurooncology and central nervous system inflammatory pathologies, a review. *Journal of cerebral blood flow and metabolism* ~~*official journal of the International Society of Cerebral Blood Flow and Metabolism*~~. 2010;30(1):15–35.

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[31] Wethington SL, Wright JD & Herzog TJ. Key role of topoisomerase I inhibitors in the treatment of recurrent and refractory epithelial ovarian carcinoma. *Expert Rev Anticancer Ther*. 2008; 8(5):819-31.

Protocol Section	Update	Rationale
Changes made throughout	Administrative changes to correct typos and formatting	N/A
Changes made throughout	Added language to distinguish between the Pilot Phase and Expansion Phase	Addition of an Expansion Phase to the protocol to further investigate the use of ferumoxytol (FMX) as an imaging diagnostic
Title	Added text “and to Predict Patient Response to Treatment”	To include an objective of the Expansion Phase, to evaluate the feasibility of ferumoxytol magnetic resonance imaging to predict patient response to treatment, in the protocol title
1 Study Synopsis	Updated to reflect amendment changes described in this document	Updated to reflect amendment changes described in this document
2 Background	Added language regarding metastatic breast cancer	To provide additional rationale for examining this patient population in the Expansion Phase of the study
2.1.4 and 2.1.5	Updated clinical trial information and safety information	Provides additional information on completed and ongoing trials, as well as new safety data obtained from a recently completed trial
2.2.3 Interaction of Ferumoxytol and MM-398	Added language regarding the Expansion Phase	Provides rationale for adding an Expansion Phase to the study
3 Study Objectives	Added objectives for the Expansion Phase	To further investigate the feasibility of ferumoxytol MRI
4 Study Design	Added language regarding the Expansion Phase	Provides information on the design of the Expansion Phase, and clarifies the Pilot Phase vs. the Expansion Phase
4.1 Enrollment and Treatment	Added language regarding the Expansion Phase	Added specific requirements for a pharmacodynamic evaluable population within the Expansion Phase, in order to ensure all appropriate data are collected to perform the analysis related to the primary objectives
5.1 Inclusion Criteria and 5.2 Exclusion Criteria	Revised and added criteria	To clarify and add criteria specific to the patient populations that will be enrolled in the Expansion Phase
5.3 Patient Discontinuation	Added language	Clarifies that patients may be discontinued from the study due to clinical and/or symptomatic deterioration
5.4 Patient Replacement	Added Section	Added specific requirements for a pharmacodynamic evaluable population within the Expansion Phase, in order to ensure all appropriate data are collected to perform the analysis related to the primary objectives
6.2.3 Administration of Ferumoxytol	Added language	To clarify that ferumoxytol will be provided by the hospital pharmacy or commercial supply
6.4 Concomitant Therapy	Added language	To clarify permitted and prohibited medications for Cohort 3 of the Expansion Phase

Protocol Section	Update	Rationale
6.4.3 Therapy for Diarrhea	Added language	To clarify that institutions may opt to follow their own guidelines for the management of diarrhea
7.1.6 Disease Evaluation; Section 7.1.6.1 Modified RECIST Criteria for Cohort 3	Added language	Language regarding the use of modified RECIST criteria was added to provide additional instructions for the evaluation of CNS disease for patients enrolled into Cohort 3 of the Expansion Phase; addition of a baseline 18F-FDG PET/CT was also added in order to identify metabolically active lesions prior to treatment
7.1.6.2 Criteria for Treatment Termination due to Progressive Disease	Added Section	To specify the reasons that patients may be discontinued from study treatment due to progressive disease per Cohort, and to allow for patients to remain on treatment under certain conditions, if the Investigator feels that the patient is deriving clinical benefit
7.2.8 Pharmacokinetic Assessments	Removed PK sampling during Ferumoxytol Phase, and edited PK timepoints during treatment and follow-up phases	Data gathered during the Pilot Phase of the study was used to inform the adjustments made to the PK sample collection time points during the Expansion Phase. Collection of PK samples during the FMX Phase is no longer required, while additional PK sampling will be performed during Cycles 2-3 of the Expansion Phase.
7.3.1.2 Expansion Phase Biopsies	Added Section	To highlight the changes made to the biopsy schedule from the Pilot Phase to the Expansion Phase; the biopsy requirement has been simplified for the Expansion Phase to require only one pre-treatment biopsy
7.4 Ferumoxytol Magnetic Resonance Imaging	Added language regarding the Expansion Phase; revised MRI time points	Data gathered during the Pilot Phase of the study was used to inform the adjustments made to the MRI time points during the Expansion Phase of the study. Tables were added to summarize the various time points for the new scan groups to which patients will be assigned during the Expansion Phase.
8.2 Expansion Phase	Schedule of Assessments added	To distinguish the different requirements in the Expansion Phase, a separate Schedule of Assessments for this phase of the study was added
10.3 Statistical Analysis	Section revised	To provide additional details on the planned analysis for the study
10.4 Study Populations	Section Added	To clarify the patient populations that will be analyzed
10.5 Disposition and Baseline Characteristics, 10.6 Efficacy Analysis, 10.7 Safety Analysis, 10.8 Biomarker Subgroup Analysis, 10.11 Sample Size	Sections revised, Section 10.3 Sample Size was moved to Section 10.11	To provide additional details, including information specific to the Expansion Phase of the study
11 Extension Phase	Section Added	To allow for any ongoing patients to continue to receive study treatment after the study analyses have been completed

Protocol Section	Change	Rationale
Entire document	Format of document updated	Updated to align with Merrimack templates and publishing guidelines
Changes made throughout	Administrative changes to correct typos and formatting	N/A
Changes made throughout	Updated Fe-MRI to FMX-MRI	FMX is the acronym for Ferumoxytol and had been used in some places in protocol and not others. Updated throughout for consistency
Changes made throughout	Added word "Completed" in sections referencing Pilot portion	Pilot portion of the study has been completed and only the Expansion phase is open to enrollment. Updated for clarity.
Title	Changed "Pilot" to "Phase 1" and added "(Nanoliposomal Irinotecan, Nal-IRI)" after MM-398	As this is a Pilot and an Expansion phase, the title was updated to reflect that it is not just a Pilot study. Generic name of MM-398 added.
1 Study Synopsis	Updated to reflect amendment changes described in this document	Updated to reflect amendment changes described in this document
2 Background	Clerical changes and grammar updates	N/A
2.1.4 MM-398 Clinical Experience	Updated clinical trial information	Provides additional information on completed and updated ongoing trials
2.1.6 MM-398 PK in Humans	Added available PK information from pilot at end of section	Provides latest available data regarding PK of MM-398 in Humans
2.2.2 Potential Toxicities of Ferumoxytol	Added language regarding Ferumoxytol safety	Based on latest available information and an updated black box warning for Ferumoxytol, this section was updated to be consistent with current drug label and to incorporate information from a Ferumoxytol Administrative Memo released with version 3.0 of the this protocol
2.3 Summary of Study Rationale	Added language regarding breast cancer expansion phase rationale	Provides clearer rationale as to why locally advanced and metastatic breast cancer was selected for the expansion phase
4.2 Study Stages and Treatment Design	Changed biopsy from pre-treatment to post-treatment and included Ferumoxytol administration update	Updated biopsy from pre-treatment to post-treatment in order to gather data on MM-398 and Ferumoxytol tumor levels. Added updated language on ferumoxytol administration as per Feraheme label
5.1 Inclusion Criteria	Updated inclusion criteria l) from ≤ 3 to ≤ 5 prior lines of chemotherapy	Based on patient populations that would be enrolled in the expansion, prior lines of chemotherapy were updated via administrative memo for version 3.0 of this protocol. Update formally incorporated into version 4.0.
5.2 Exclusion Criteria	Revised and added criteria	To clarify and add criteria specific to the patient populations that will be enrolled in the expansion
6.1 Description of MM-398	Updated fill volume	Packaging of clinical trial IP changed from 9.5mL to 10mL

Protocol Section	Change	Rationale
6.1.1 Storage and Handling of MM-398	Changed 6 hours at room temperature to 4 hours at room temperature	Updated to reflect latest stability data and the Pharmacy manual
6.1.3 Administration of MM-398	Added language	Able to clarify this section based on latest information regarding study drug
6.1.5.10 Other Potential Toxicities	Added language	To clarify treatment for QTc prolongation and guidance on resuming study treatment
6.2.3 Administration of Ferumoxytol	Added updated safety and administration information	To reflect update to Feraheme label and black box warning for hypersensitivity. This language was released to sites as an administrative memo when information became known. Now formally incorporated into V 4.0
6.2.4 Important Treatment Considerations with Ferumoxytol	Added "Additional Information for Health Care Professionals" and AESI requirement for capturing Adverse Events related to FMX	To reflect update to Feraheme label and black box warning for hypersensitivity. This language was released to sites as an administrative memo when information became known. Now formally incorporated into V 4.0. Enhanced safety reporting for ferumoxytol.
7.3.1.2 Expansion Phase Biopsies	Changed biopsy requirement from pre-treatment to 72 hrs post-treatment	To highlight the changes made to the biopsy schedule; biopsy requirement updated to gather more information and to fit into the current patient visit schedule to ease scheduling and patient burden. Information added on assays and data to be gathered
7.3.2 Archived Tumor Samples	Added language	Incorporated language regarding return of archived samples to sites and potential uses/assays for the archived samples
7.4 Ferumoxytol Magnetic Resonance Imaging	Clerical changes to body and Tables.	Minor changes to improve clarity of this section
8 Schedule of Assessments	Pilot Schedule of Assessments chart removed. Expansion chart updated	Pilot Phase Schedule of Assessments removed as the pilot phase is closed and to avoid confusion for site staff. Expansion phase chart updated to reflect changes to biopsy requirement and simplification of schedule based on information already communicated to sites via administrative memos.
9.1.3 Adverse Events of Special Interest	New section	Section added to capture requirements for reporting adverse events related to ferumoxytol administration as AESIs.
9.1.4 Serious Adverse Event	Added language regarding death due to disease progression	To clarify classification of death due to disease progression as well as reporting requirements in such an event
End of Table		

Summary of Changes

Protocol MM-398-01-01-02: A Phase 1 Study in Patients Treated with MM-398 (Nanoliposomal Irinotecan, nal-IRI,) to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages and to Predict Patient Response to Treatment

	Version No:	Version Date
Current Protocol	4	21Jul2016
Amended Protocol	5	03Nov2016

General Changes and Note

Protocol Amendment 5 reduced the starting dose of MM-398 to 60 mg/m^2 from 80 mg/m^2. Additionally, information regarding the allowance for dose escalation of MM-398 from 60 mg/m^2 to 80 mg/m^2 was added. Dose modifications for adverse events in section 6.1.6.1 and 6.1.6.2 were changed to reflect this change.

The rationale for the change in starting dose is that during a recent review of the safety data collected in the study after 16 patients have been enrolled in the breast expansion cohort, it was noted that the gastrointestinal serious adverse events (e.g. nausea, vomiting, diarrhea and ileitis) occurred at a frequency of 36% in the breast cancer expansion cohort, while any grade diarrhea and grade 3 or higher diarrhea were reported at 64% and 27% respectively. When comparing the gastrointestinal toxicity profile in the breast cancer expansion cohort in this study to the MM-398 pivotal NAPOLI-1 study in patients with metastatic pancreatic cancer who progressed following gemcitabine-based therapy, no major differences were noted between a) the female Caucasian subgroup of the NAPOLI-1 study and b) the current cohort in terms of frequency or severity of gastrointestinal adverse events (e.g. any grade diarrhea 73%, grade 3 or higher diarrhea 27% and gastrointestinal SAEs 23% in the NAPOLI-1 study in the female Caucasian subgroup treated with the MM-398-5-FU/LV combination [n=30]). It is relevant to note, that in the NAPOLI-1 study, the Caucasian female population had the highest frequency and severity of diarrhea and gastrointestinal serious adverse events as opposed other gender and race groups (such as the Caucasian male, Asian female or Asian male). Therefore, for the population under study in the ongoing breast cancer expansion cohort in the MM-398-01-01-02 study that is currently conducted in the United States, the starting dose of MM-398 will be lowered to 60 mg/m^2 with the allowance for dose escalation to 80 mg/m^2 in subsequent doses. This modification is anticipated to increase the tolerability of the MM-398 regimen under study in this patient population.

Alignment of the starting dose for patients with UGT1A1*28 homozygosity with non-homozygous patients was made because, based on population PK analysis of data collected on patients dosed with nal-IRI, there is an absence of a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure or toxicity following nal-IRI administration. UGT1A1*28 status will continue to be collected on all patients as a safety biomarker to further analyze the association between UGT1A1*28 homozygosity, SN-38 concentration and toxicity. Dose modifications for UGT1A1*28 homozygous patients were changed to align with the above changes made.

Additional changes made:

- The schedule of events table to account for clerical errors within the footnotes of the table.
- Exclusion criteria a. was amended to allow patients with sub-centimeter, asymptomatic lesions to participate in the study.
- MRI Imaging Scan Time Points tables (Tables 14 and 15) were changed per recent memo to reflect appropriate timepoints.
- Lastly, a maximum year of specimen storage was added.

Section No. or Title	Current Protocol Text: Version 4	Amended Protocol Text: Version 5	Rationale
Synopsis (Study Design)	There are four stages to this study: • Screening Period (-28 d): patients undergo screening assessments to determine if they are eligible for the study • Ferumoxytol Period (Day 1 – Day 2): patients receive ferumoxytol (FMX) infusion and undergo required FMX-MRI scans and prior to receiving MM-398 • MM-398 Treatment Period (C1D1 – progression of disease): patients receive an MM-398 dose of 80 mg/m2 every 2 weeks, other required assessments, and a post-treatment biopsy 72 hours after first dose of MM-398 • Follow Up Period (+30 d from last dose): patients return to clinic 30 days following the last dose of MM-398 for final safety assessments MM-398 will be administered at a dose of 80 mg/m2 every two weeks and patients will be treated until disease progression or unacceptable toxicity.	There are four stages to this study: • Screening Period (-28 d): patients undergo screening assessments to determine if they are eligible for the study • Ferumoxytol Period (Day 1 – Day 2): patients receive ferumoxytol (FMX) infusion and undergo required FMX-MRI scans and prior to receiving MM-398 • MM-398 Treatment Period (C1D1 – progression of disease): patients receive an MM-398 starting dose of 60 mg/m2 every 2 weeks which should be dose escalated to 80 mg/m2 every 2 weeks in subsequent doses depending on patient tolerance , other required assessments, and a post-treatment biopsy 72 hours after first dose of MM-398 • Follow Up Period (+30 d from last dose): patients return to clinic 30 days following the last dose of MM-398 for final safety assessments MM-398 will be administered at a dose of 60 mg/m2 every two weeks and patients will be treated until disease progression or unacceptable toxicity. The dose of MM-398 should be escalated to 80 mg/m2 every two weeks depending on patient tolerance.	Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.
Synopsis (Exclusion Criteria)	a) Active central nervous system metastases, indicated by clinical symptoms, cerebral edema, steroid requirement, or progressive disease (applies to Pilot Phase and Expansion Phase Cohorts 1-2 only)	a) Active central nervous system metastases, indicated by clinical symptoms, cerebral edema, or steroid requirement (applies to Pilot Phase and Expansion Phase Cohorts 1-2 only)	Removed "progressive disease" to allow patients with sub-centimeter,

Section No. or Title	Current Protocol Text: Version 4	Amended Protocol Text: Version 5	Rationale
			asymptomatic lesions to participate.
Synopsis (Study Treatment)	MM-398 monotherapy will be administered by intravenous (IV) infusion over 90 minutes at a dose of 80 mg/m^2 every two weeks.	MM-398 monotherapy will be administered by intravenous (IV) infusion over 90 minutes at a dose of 60 mg/m^2 every two weeks. The dose of MM-398 should be escalated to 80 mg/m^2 in subsequent doses depending on tolerance.	Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.
4.2 Study Stages and Treatment Design	MM-398 Treatment Period (C1D1 – progression of disease): patients receive an MM-398 dose of 80 mg/m^2 every 2 weeks, other required assessments, and undergo a post-treatment (MM-398) multiple pass core biopsy	MM-398 Treatment Period (C1D1 – progression of disease): patients receive an MM-398 dose of 60 mg/m^2 every 2 weeks, which should be dose escalated to 80 mg/m^2 every 2 weeks in subsequent doses depending on patient tolerance, other required assessments, and undergo a post-treatment (MM-398) multiple pass core biopsy	Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.
4.2 Study Stages and Treatment Design	MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of 80 mg/m2 every two weeks. The MM-398 period (C1D1) should begin within 7 days of the ferumoxytol infusion.	MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of60 mg/m2 every two weeks. The MM-398 period (C1D1) should begin within 7 days of the ferumoxytol infusion. The dose of MM-398 should be escalated to 80 mg/m2 every two weeks depending on patient tolerance.	Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.
5.2 Exclusion Criteria	a) Active central nervous system metastases, indicated by clinical symptoms, cerebral edema, steroid requirement, or progressive disease (applies to Pilot Phase and Expansion Phase Cohorts 1-2 only)	a) Active central nervous system metastases, indicated by clinical symptoms, cerebral edema, or steroid requirement (applies to Pilot Phase and Expansion Phase Cohorts 1-2 only)	Removed "progressive disease" to allow patients with sub-centimeter, asymptomatic lesions to participate.

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
Version 4</th><th>Amended Protocol Text:
Version 5</th><th>Rationale</th></tr>
<tr><td>6.1.3 Administration of MM-398</td><td>MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of 80 mg/m2 every two weeks. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.</td><td>MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of60 mg/m2 every two weeks. The dose of MM-398 should be escalated to 80 mg/m2 every two weeks depending on patient tolerance. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.</td><td>Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.</td></tr>
<tr><td>6.1.6.1 Hematologic Toxicities (Table 7)</td><td>
<table>
<tr><th>Worst CTCAE Grade</th><th>ANC Levels (cells/mm^3)</th><th>Modification</th></tr>
<tr><td>Grade 1 or 2</td><td>1000 - 1999</td><td>Same as previous dose</td></tr>
<tr><td>Grade 3 or 4</td><td>< 1000</td><td>Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.</td></tr>
</table>
</td><td>
<table>
<tr><th rowspan="2">Worst CTC AE Grade</th><th rowspan="2">ANC Levels (cells/mm^3)</th><th colspan="3">Modification</th></tr>
<tr><th>Occurrence</th><th>MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)</th><th>MM-398 adjustment in patients receiving 80 mg/m^2 (if dose escalated after first dose)</th></tr>
<tr><td>Grade 1 or 2</td><td>1000-1999</td><td>Any</td><td>Same as previous dose</td><td>Same as previous dose</td></tr>
<tr><td rowspan="3">Grade 3 or 4</td><td rowspan="3"><1000</td><td>First</td><td>50 mg/m^2</td><td>60 mg/m^2</td></tr>
<tr><td>Second</td><td>40 mg/m^2</td><td>50 mg/m^2</td></tr>
<tr><td>Third</td><td>Discontinue from MM-398</td><td>Discontinue from MM-398</td></tr>
</table>
</td><td>Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.</td></tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
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Version 5</th><th>Rationale</th></tr>
<tr>
<td>6.1.6.1 Hematologic Toxicities (Table 8)</td>
<td>
<table>
<tr><th>Worst CTCAE Grade</th><th>Modification</th></tr>
<tr><td>< Grade 2</td><td>Same as previous dose</td></tr>
<tr><td>Grade 3 or 4</td><td>Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.</td></tr>
</table>
</td>
<td>
<table>
<tr><th rowspan="2">Worst CTCAE Grade</th><th colspan="3">Modification</th></tr>
<tr><th>Occurrence</th><th>MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)</th><th>MM-398 adjustment in patients with dose escalation 80 mg/m^2</th></tr>
<tr><td>Grade 1 or Grade 2</td><td>Any</td><td>Same as previous dose</td><td>Same as previous dose</td></tr>
<tr><td rowspan="3">Grade 3 or 4</td><td>First</td><td>50 mg/m^2</td><td>60 mg/m^2</td></tr>
<tr><td>Second</td><td>40 mg/m^2</td><td>50 mg/m^2</td></tr>
<tr><td>Third</td><td>Discontinue from MM-398</td><td>Discontinue from MM-398</td></tr>
</table>
</td>
<td>Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.</td>
</tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
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Version 5</th><th>Rationale</th></tr>
<tr>
<td>6.1.6.2 Non-hematologic Toxicities (Table 9)</td>
<td>
<table>
<tr><th>Worst CTCAE Grade</th><th>Description</th><th>Modification</th></tr>
<tr><td>Grade 1</td><td>2-3 stools/day > pretreatment</td><td>Same as previous dose</td></tr>
<tr><td>Grade 2</td><td>4-6 stools/day > pretreatment</td><td>Same as previous dose</td></tr>
<tr><td>Grade 3</td><td>7-9 stools/day > pretreatment</td><td>Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.</td></tr>
<tr><td>Grade 4</td><td>>10 stools/day > pretreatment</td><td>Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.</td></tr>
</table>
</td>
<td>
<table>
<tr><th rowspan="2">Worst CTCAE Grade</th><th colspan="3">Modification</th></tr>
<tr><th>Occurrence</th><th>MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)</th><th>MM-398 adjustment in patients with dose escalation 80 mg/m^2</th></tr>
<tr><td>Grade 1 or Grade 2</td><td>Any</td><td>Same as previous dose</td><td>Same as previous dose</td></tr>
<tr><td rowspan="3">Grade 3 or 4</td><td>First</td><td>50 mg/m^2</td><td>60 mg/m^2</td></tr>
<tr><td>Second</td><td>40 mg/m^2</td><td>50 mg/m^2</td></tr>
<tr><td>Third</td><td>Discontinue from MM-398</td><td>Discontinue from MM-398</td></tr>
</table>
</td>
<td>Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.</td>
</tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
Version 4</th><th>Amended Protocol Text:
Version 5</th><th>Rationale</th></tr>
<tr>
<td>6.1.6.2 Non-hematologic Toxicities (Table 10)</td>
<td>
<table>
<tr><th>Worst CTCAE Grade</th><th>Modification</th></tr>
<tr><td>Grade 1 or 2</td><td>Same as previous dose</td></tr>
<tr><td>Grade 3 or 4 (except nausea and vomiting)</td><td>Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.</td></tr>
<tr><td>Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy</td><td>Optimize anti-emetic therapy AND reduce dose to 60 mg/m^2; if the patient is already receiving 60 mg/m^2, reduce dose to 50 mg/m^2. Patient should be withdrawn if reductions lower than 50 mg/m^2 are required.</td></tr>
</table>
</td>
<td>
<table>
<tr><th rowspan="2">Worst CTC AE Grade</th><th colspan="3">Modification</th></tr>
<tr><th>Occurrence</th><th>MM-398 adjustment in patients receiving 60 mg/m^2 (and have not been escalated to 80 mg/m^2)</th><th>MM-398 adjustment in patients with dose escalation 80 mg/m^2</th></tr>
<tr><td>Grade 1 or 2</td><td>Any</td><td>Same as previous dose</td><td>Same as previous dose</td></tr>
<tr><td rowspan="3">Grade 3 or 4 (except nausea and vomiting)</td><td>First</td><td>50 mg/m^2</td><td>60 mg/m^2</td></tr>
<tr><td>Second</td><td>40 mg/m^2</td><td>50 mg/m^2</td></tr>
<tr><td>Third</td><td>Discontinue from MM-398</td><td>Discontinue from MM-398</td></tr>
<tr><td rowspan="3">Grade 3 or 4 nausea and/or vomiting[a]</td><td>First</td><td>50 mg/m^2</td><td>60 mg/m^2</td></tr>
<tr><td>Second</td><td>40 mg/m^2</td><td>50 mg/m^2</td></tr>
<tr><td>Third</td><td>Discontinue from MM-398</td><td>Discontinue from MM-398</td></tr>
</table>
[a]For Grade 3 or 4 nausea and vomiting, dose reduce only if they occur despite optimal anti-emetic therapy
</td>
<td>Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.</td>
</tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
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Version 5</th><th>Rationale</th></tr>
<tr><td>6.1.6.3</td><td>6.1.6.3 UGT1A1*28 Positive Patients
Patients will be tested for UGT1A1*28 status at screening. The result of the test is not required prior to the initial dose of MM-398. , but future doses may be reduced for patients positive for UGT1A1*28. Depending on the overall safety profile seen after the first dose, the dose may be reduced to 60 mg/m2 or 40 mg/ m2, after discussion between the PI, Sponsor and Medical Monitor</td><td>6.1.6.3 UGT1A1*28 Homozygous Patients
Patients will be tested for UGT1A1*28 status at screening. The result of the test is not required prior to the initial dose of MM-398. Both the starting dose and dose modification will be the same for all patients regardless of UGT1A1*28 genotype.</td><td>The word “positive” was changed for “homozygous” at it is a more accurate description of these patients.</td></tr>
<tr><td>6.4.3 Therapy of Diarrhea (Table 11)</td><td><table>
<tr><th>Clinical Presentation</th><th>Intervention</th></tr>
<tr><td>Diarrhea, any grade</td><td>Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea; 2 mg every 4 hours for 5-FU induced diarrhea): continue until diarrhea-free for ≥ 12 hours</td></tr>
<tr><td>Diarrhea persists on loperamide for > 24 hours</td><td>Oral fluoroquinolone x 7 days</td></tr>
<tr><td>Diarrhea persists on loperamide for > 48 hours</td><td>Stop loperamide; hospitalize patient; administer IV fluids</td></tr>
<tr><td>ANC < 500 cells/µL, regardless of fever or diarrhea</td><td>Oral fluoroquinolone (continue until resolution of neutropenia)</td></tr>
<tr><td>Fever with persistent diarrhea, even in the absence of neutropenia</td><td>Oral fluoroquinolone (continue until resolution of fever and diarrhea)</td></tr>
</table></td><td><table>
<tr><th>Clinical Presentation</th><th>Intervention</th></tr>
<tr><td>Diarrhea, any grade</td><td>Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea): continue until diarrhea-free for ≥ 12 hours</td></tr>
<tr><td>Diarrhea persists on loperamide for > 24 hours</td><td>Oral fluoroquinolone x 7 days</td></tr>
<tr><td>Diarrhea persists on loperamide for > 48 hours</td><td>Stop loperamide; hospitalize patient; administer IV fluids</td></tr>
<tr><td>ANC < 500 cells/µL, regardless of fever or diarrhea</td><td>Oral fluoroquinolone (continue until resolution of neutropenia)</td></tr>
<tr><td>Fever with persistent diarrhea, even in the absence of neutropenia</td><td>Oral fluoroquinolone (continue until resolution of fever and diarrhea)</td></tr>
</table></td><td>Rationale for reducing the starting dose of MM-398 is outlined on the first page of this document.</td></tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
Version 4</th><th>Amended Protocol Text:
Version 5</th><th>Rationale</th></tr>
<tr><td>7.2.5 UGT1A1*28</td><td>A whole blood sample will be collected from all patients at baseline to test for UGT1A1*28 allele status. The result is not needed prior to the initial dose of MM-398, but subsequent doses of MM-398 may be reduced for patients positive for UGT1A1*28, as described in Section Error! Reference source not found..</td><td>A whole blood sample will be collected from all patients at baseline to test for UGT1A1*28 allele status. The result is not needed prior to the initial dose of MM-398. Both the starting dose and dose modification will be the same for all patients regardless of UGT1A1*28 genotype, as described in Section 6.1.6.3.</td><td>Rationale for having same starting dose, irrespective of UGT1A1 genotype is outlined on the first page of this document.</td></tr>
<tr><td>7.4 Ferumoxytol Magnetic Resonance Imaging (Table 14)</td><td>
<table>
<tr><th>Scan Group</th><th>N[a]</th><th>Baseline</th><th>Baseline (repeat)</th><th>1 - 4 h</th><th>24 h (16 -24 h)</th><th>24 h (repeat)</th><th>2 wk (+/- 1 Day) Baseline</th></tr>
<tr><td>1</td><td>5</td><td>X</td><td>X</td><td></td><td></td><td>X</td><td>X</td></tr>
<tr><td>2</td><td>5</td><td>X</td><td></td><td></td><td>X</td><td>X</td><td></td></tr>
<tr><td>3</td><td>10</td><td>X</td><td></td><td></td><td>X</td><td>X</td><td></td></tr>
</table>
a. Enrollment into Scan Groups 1 and 2 may be increased at the discretion of the Sponsor, in the event that any of the images are not evaluable, or it is determined that more information is needed from the additional scan time points. In this case, enrollment into Scan Group 3 will be decreased by a corresponding number of patients.</td><td>
<table>
<tr><th>Scan Group</th><th>N[a]</th><th>Baseline</th><th>Baseline (repeat)</th><th>1-4 h</th><th>24 h (16-24 h)</th><th>24 h (repeat)</th><th>2 wk (+/- 1 Day) Baseline</th></tr>
<tr><td>1</td><td>5</td><td>X</td><td>X</td><td></td><td>X</td><td></td><td>X</td></tr>
<tr><td>2</td><td>5</td><td>X</td><td></td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>3</td><td>10</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td></td></tr>
</table>
a. Enrollment into Scan Groups 1 and 2 may be increased at the discretion of the Sponsor, in the event that any of the images are not evaluable, or it is determined that more information is needed from the additional scan time points. In this case, enrollment into Scan Group 3 will be decreased by a corresponding number of patients.</td><td>Clerical issues with the table were resolved to match the imaging manual.</td></tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
Version 4</th><th>Amended Protocol Text:
Version 5</th><th>Rationale</th></tr>
<tr><td>7.4 Ferumoxytol Magnetic Resonance Imaging (Table 15)</td><td>
<table>
<tr><th>Scan Group</th><th>N</th><th>Baseline</th><th>Baseline (repeat)</th><th>1 - 4 h</th><th>24 h (16 -24 h)</th><th>24 h (repeat)</th><th>2 wk (+/- 1 Day) Baseline</th></tr>
<tr><td>4 (cohort 3)</td><td>10</td><td>X[a]</td><td></td><td></td><td>X[b]</td><td>X[a]</td><td>X</td></tr>
</table>
a. Patients with extra-cranial disease will have MRIs of two body areas at baseline and 24 h: one brain scan and one body scan (body scan will capture the majority of the patient's extra-cranial disease; see imaging manual for details)
b. Brain scan only will be completed at this time point
</td><td>
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a. Patients with extra-cranial disease will have MRIs of two body areas at baseline and 24 h: one brain scan and one body scan (body scan will capture the majority of the patient's extra-cranial disease; see imaging manual for details)
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</td><td>Clerical issues with the table were resolved to match the imaging manual.</td></tr>
<tr><td>8.2 Expansion Phase (Schedule of Assessments)</td><td>Table Footnotes:
1. Procedures to be completed within 28 days of ferumoxytol dose
2. Procedures to be completed within 7 days of ferumoxytol dose
3. Body weight to be collected within 7 days of ferumoxytol dose
4. Two independent readings at least 1 minute apart
5. Procedure completed at Cycle 2 only
6. One reading prior to the start of the MM-398 infusion and one reading post infusion of MM-398 is required
7. Two FMX-MRI collected as outlined in Section Error! Reference source not found. and Error! Reference source not found. and Error! Reference source not found.</td><td>Table Footnotes:
1. Procedures to be completed within 28 days of ferumoxytol dose
2. Procedures to be completed within 7 days of ferumoxytol dose
3. Body weight to be collected within 7 days of ferumoxytol dose
4. Two independent readings at least 1 minute apart
5. Two FMX-MRI collected as outlined in Section Error! Reference source not found. and Error! Reference source not found. and Error! Reference source not found.
6. One MRI at 24 h (16-24 hour window) except Scan Group 2, who will undergo 2 repeat scans at the 24 h timepoint
7. For Scan Group 1 only, one MRI scan</td><td>Clerical issues with the footnotes were resolved to match appropriately</td></tr>
</table>

Section No. or Title	Current Protocol Text: Version 4	Amended Protocol Text: Version 5	Rationale
	8. One MRI at 24 h (16-24 hour window) except Scan Group 2, who will undergo 2 repeat scans at the 24 h timepoint 9. For Scan Group 1 only, one MRI scan will be performed during Cycle 1 only (±1 day) 10. Biopsy required for Cohorts 1 and 2, as well as Cohort 3 patients with extracranial disease that can be safely biopsied 11. Post-Treatment Biopsy collected 72h post C1D1 MM-398 infusion 12. Collection of archived tumor block or paraffin embedded slides, if available 13. Samples collected at the following timepoints on C1D1 of the MM-398 Treatment Phase: just prior to the MM-398 infusion (-5 mins); at the end of the MM-398 infusion (+5 mins); +2 hours after the completion of the MM-398 infusion (±30 mins); 14. Sample collected +48 hours after the completion of the MM-398 infusion (±24 hours) 15. Sample collected +168 hours/7 days after the completion of the MM-398 infusion (±24 hours) 16. Sample obtained just prior to dosing with MM-398 (-24 hour window) 17. MM-398 administration should occur ±2 days from scheduled date of administration 18. In addition to normal labs, iron levels	will be performed during Cycle 1 only (±1 day) 8. Biopsy required for Cohorts 1 and 2, as well as Cohort 3 patients with extracranial disease that can be safely biopsied 9. Post-Treatment Biopsy collected 72h post C1D1 MM-398 infusion 10. Collection of archived tumor block or paraffin embedded slides, if available 11. Samples collected at the following timepoints on C1D1 of the MM-398 Treatment Phase: just prior to the MM-398 infusion (-5 mins); at the end of the MM-398 infusion (+5 mins); +2 hours after the completion of the MM-398 infusion (±30 mins); 12. Sample collected +48 hours after the completion of the MM-398 infusion (±24 hours) 13. Sample collected +168 hours/7 days after the completion of the MM-398 infusion (±24 hours) 14. Sample obtained just prior to dosing with MM-398 (-24 hour window) 15. MM-398 administration should occur ±2 days from scheduled date of administration 16. In addition to normal labs, iron levels will be measured at the screening visit, at the time of the first MM-398 dose of Cycle 2 (first additional cycle) and at the 30 Day Follow-up visit. 17. Result not required prior to enrollment in the study. Both the starting dose and dose	

Section No. or Title	Current Protocol Text: Version 4	Amended Protocol Text: Version 5	Rationale
	will be measured at the screening visit, at the time of the first MM-398 dose of Cycle 2 (first additional cycle) and at the 30 Day Follow-up visit. 19. Result not required prior to enrollment in the study, but patients positive for UGT1A1*28 may have future doses reduced as described in Section **Error! Reference source not found.** 20. Blood will be collected for biomarker analyses 21. Unless completed in the prior 6 weeks 22. Disease evaluations should be done every 8 weeks (± 7 days) after 1st dose 23. Visit for samples should be obtained ± 2 days from scheduled date of collection 24. The 30-Day Follow-Up visit should occur 30 days (± 7 days) after last dose 25. The Cycle 1 Day 1 visit should occur within 7 days of ferumoxytol infusion 26. In addition to contrast-enhanced CT and/or MRI, 18F-FDG PET/CT scan required at baseline only (patients with extracranial disease only) 27. Administer while patient is in a reclined or semi-reclined position. Patients should be closely monitored for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse	modification will be the same for all patients regardless of UGT1A1*28 genotype, as described in Section **Error! Reference source not found.** 18. Blood will be collected for biomarker analyses 19. Unless completed in the prior 6 weeks 20. Disease evaluations should be done every 8 weeks (± 7 days) after 1st dose 21. Visit for samples should be obtained ± 2 days from scheduled date of collection 22. The 30-Day Follow-Up visit should occur 30 days (± 7 days) after last dose 23. The Cycle 1 Day 1 visit should occur within 7 days of ferumoxytol infusion 24. In addition to contrast-enhanced CT and/or MRI, ^{18}F-FDG PET/CT scan required at baseline only (patients with extracranial disease only) 25. Administer while patient is in a reclined or semi-reclined position. Patients should be closely monitored for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during administration and for at least 30 minutes following the infusion as per the ferumoxytol label instructions. Ferumoxytol administration outlined in Section **Error! Reference source not found.**.	

Section No. or Title	Current Protocol Text: Version 4	Amended Protocol Text: Version 5	Rationale
	during administration and for at least 30 minutes following the infusion as per the ferumoxytol label instructions. Ferumoxytol administration outlined in Section **Error! Reference source not found.**.		
12.8 Confidentiality of Biomarker Samples	Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens will be stored indefinitely. At the time of informed consent, patients will be able to refuse indefinite storage of these remaining samples. If indefinite storage is refused, any remaining samples will be destroyed following the initial specified analyses.	Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens will be stored for a maximum of 5 years after study completion. At that time, any remaining samples will be destroyed. At the time of informed consent, patients will be able to refuse long-term storage of these remaining samples. If long-term storage is refused, any remaining samples will be destroyed following the initial specified analyses.	The addition of the maximum year storage being added is to provide clarity to the patients on how long their samples will be stored for
12.8 Confidentiality of Biomarker Samples	Any samples that a patient consents to be stored indefinitely may be used by the Sponsor for future research.	Any samples that a patient consents to long-term storage may be used by the Sponsor for future research.	"Indefinitely" was removed to align with the new maximum storage years of specimens