(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 June 2016 (16.06.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/094402 A1

(51) International Patent Classification:
A61K 31/436 (2006.01) *A61K 35/04* (2006.01)
A61K 9/127 (2006.01)

(21) International Application Number:
PCT/US2015/064491

(22) International Filing Date:
8 December 2015 (08.12.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/089,685 9 December 2014 (09.12.2014) US

(71) Applicant: **MERRIMACK PHARMACEUTICALS, INC.** [US/US]; One Kendall Square, Suite B7201, Cambridge, MA 02139 (US).

(72) Inventors: **BAYEVER, Eliel**; 10 Rogers Street, Cambridge, MA 02142 (US). **FITZGERALD, Jonathan, Basil**; 32 Magnolia Street, Arlington, MA 02474 (US). **KIM, Jaeyeon**; 30 Donald Street, Lexington, MA 02420 (US). **KLINZ, Stephan**; 132 Wilson Street, Norwood, MA 02062 (US).

(74) Agent: **BOTT, Cynthia, M.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, MI 49007 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with amended claims and statement (Art. 19(1))*

(54) Title: TREATMENT OF BREAST CANCER WITH LIPOSOMAL IRINOTECAN

(57) Abstract: Provided are methods for treating breast cancer in a patient by administering effective amounts of liposomal irinotecan sucrosofate (MM-398). The breast cancer may be triple negative breast cancer (TNBC), estrogen receptor/progesterone receptor (ER/PR) positive breast cancer, ER-positive breast cancer, or PR-positive breast cancer, or metastatic breast cancer.

WO 2016/094402 A1

TREATMENT OF BREAST CANCER WITH LIPOSOMAL IRINOTECAN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/089,685, filed December 9, 2014, the entire contents of which are incorporated herein by reference in their entirety.

BACKGROUND

Irinotecan (also known as CPT-11) is a highly effective chemotherapeutic agent that, in the form of irinotecan hydrochloride, was approved nearly 20 years ago for the treatment of colorectal cancer. Irinotecan is an active prodrug that is converted in a much more active metabolite known as SN-38 by the action of a carboxylesterase enzyme. In tumors, this carboxylesterase activity is locally concentrated in tumor associated macrophages (TAMs).

MM-398 is a novel liposomally encapsulated preparation of irinotecan sucrosofate. The MM-398 nanoliposomal delivery system is designed to reduce systemic exposure and increase drug accumulation within tumors through the enhanced permeability and retention effect that results from the disorganized and leaky characteristics of tumor vasculature. MM-398 liposomes have been engineered with the aim of optimally exploiting the propensity of TAMs to take up liposomes and to thereby maximize activation of irinotecan to yield intratumoral SN-38. These factors contribute to altering systemic exposure and distribution of MM-398 as compared to irinotecan hydrochloride. Accordingly, safe and effective dosing of MM-398 is not the same as, and its side effect profile differs from that of irinotecan hydrochloride. The altered systemic exposure and distribution of MM-398 is designed to provide an opportunity to administer irinotecan therapy to cancer patients for whom irinotecan hydrochloride cannot be safely dosed in amounts required to provide effective therapy.

One group of cancer patients who would benefit from safe and effective dosing of irinotecan is breast cancer patents, for whom irinotecan hydrochloride has not proven adequately safe and effective to be approved for routine use. The present disclosure provides uses, dosing and administration parameters, methods of use and other factors for treating breast cancer with MM-398, and thereby address the need for new, effective treatments for breast cancer, and provides additional benefits.

SUMMARY

Provided are methods for treating breast cancer in a patient, the methods comprising administering to the patient liposomal irinotecan (for example, irinotecan sucrose octasulfate salt

CSPC Exhibit 1026
Page 2 of 42

liposome injection, also referred to as nal-IRI, PEP02, MM-398, or ONIVYDE) according to a particular clinical dosage regimen. Provided too is the use of MM-398 for the safe and effective treatment of breast cancer. Compositions adapted for use in such methods are also provided.

In one aspect, a method for treatment (*i.e.*, effective treatment) of a breast cancer tumor, in a patient (in other words, a use of MM-398) is provided, the method (or use) comprising: administering to the patient an effective amount of liposomal irinotecan in the form of MM-398. In one embodiment, the breast cancer is: a) HER2 negative breast cancer, or b) HER2 negative metastatic breast cancer, or c) HER2 negative or HER2 positive and is metastatic breast cancer with at least one brain lesion. In one embodiment, the brain lesion is a progressive brain lesion. In another embodiment, the administration is carried out in at least one cycle, wherein the cycle is a period of 2 weeks and the irinotecan is administered once per cycle on day 1 of each cycle, and wherein for at least a first cycle the irinotecan is administered at a dose of at least 60 mg/m^2 or at least 80 mg/m^2. In one embodiment, the dose is 80 mg/m^2. In another embodiment, at least the first cycle the irinotecan is administered at a dose of 80, 100, 120, 150, 180, 210, or 240 mg/m^2. In a particular embodiment, at least the first cycle the irinotecan is administered at a dose of 80 mg/m^2.

In one embodiment, the administration is carried out in at least two cycles and, if the patient is positive (homozygous) for the UGT1A1*28 allele, the dose following the first cycle is 20 mg/m^2 or 40 mg/m^2 lower than the dose given in the first cycle and if the patient is negative for the UGT1A1*28 allele, the dose following the first cycle is the same as the dose given in the first cycle. In another embodiment, all administrations following the first cycle are at the same dose.

In one embodiment, the breast cancer is triple negative or basal-like breast cancer. In another embodiment, the breast cancer is ER-positive, PR-positive, or ER/PR-positive breast cancer. In yet another embodiment, the breast cancer is metastatic breast cancer. In another embodiment, the patient does not have any brain lesions and the breast cancer is HER2 0+ or 1+ by immunohistochemistry, HER2 negative by *in situ* hybridization, or HER2 negative by dual-probe *in situ* hybridization. In another embodiment, prior to each administration of the irinotecan, the patient is pre-medicated with either or both of 1) dexamethasone and 2) either a 5-HT3 antagonist or another anti-emetic. In one embodiment, the irinotecan is administered intravenously over 90 minutes. In another embodiment, the administration of the irinotecan, an effective amount of at least one anti-cancer agent other than irinotecan is co-administered to the patient.

In one embodiment, the treatment results in a positive outcome in the patient. In one embodiment, the positive outcome is partial complete response (pCR), complete response (CR),

CSPC Exhibit 1026
Page 3 of 42

partial response (PR), or stable disease (SD). In another embodiment, the positive outcome is a reduction in: a) tumor size, b) tumor infiltration into peripheral organs, c) tumor metastasis or d) recurrence of tumor. In one embodiment, prior to treatment with the irinotecan, the patient receives a ferumoxytol infusion followed by an MRI scan.

In another aspect is provided a kit for treating a breast cancer in a human patient, the kit comprising a container holding 1) a second container holding at least one dose of MM-398 and 2) instructions for using the irinotecan according to the methods and uses disclosed herein.

DETAILED DESCRIPTION

I. Definitions

As used herein, a "patient" is a human cancer patient.

As used herein, "effective treatment" refers to treatment producing a beneficial effect, *e.g.*, amelioration of at least one symptom of a disease or disorder. A beneficial effect can take the form of an improvement over baseline, i.e., an improvement over a measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of a cancer. Effective treatment may refer to alleviation of at least one symptom of a cancer. Such effective treatment may, *e.g.*, reduce patient pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a cancer tumor, and/or may slow growth of a cancer tumor.

The term “effective amount” refers to an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay tumor development. In some embodiments, an effective amount is an amount sufficient to prevent or delay tumor recurrence. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition may do any one or any combination of (i) through (vii) as follows: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and may stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

CSPC Exhibit 1026
Page 4 of 42

The terms "co-administration," "co-administered," "concomitant administration" or minor variations of these terms, indicate administration of at least two therapeutic agents to a patient either simultaneously or sequentially within a time period during which the first administered therapeutic agent is still present in the patient when the second administered therapeutic agent is administered.

"Dosage" refers to parameters for administering a drug in defined quantities per unit time (*e.g.*, per hour, per day, per week, per month, etc.) to a patient. Such parameters include, *e.g.*, the size of each dose. Such parameters also include the configuration of each dose, which may be administered as one or more units, *e.g.*, taken at a single administration, *e.g.*, orally (*e.g.*, as one, two, three or more pills, capsules, etc.) or injected (*e.g.*, as a bolus). Dosage sizes may also relate to doses that are administered continuously (*e.g.*, as an intravenous infusion over a period of minutes or hours). Such parameters further include frequency of administration of separate doses, which frequency may change over time.

"Dose" refers to an amount of a drug given in a single administration.

"Liposomal Irinotecan" refers to a formulation of the chemotherapy drug irinotecan wherein the irinotecan is encapsulated within a phospholipid bilayer. Examples of liposomal irinotecan include, for example, MM-398 (Merrimack Pharmaceuticals, Inc.) and IHL-305 (Yakult Honsha Co., LTD.).

As used herein, "cancer" refers to a condition characterized by abnormal, unregulated, malignant cell growth. In one embodiment, the cancer is pathologically characterized by a solid tumor, *e.g.*, a breast cancer, *e.g.*, triple negative breast cancer (TNBC, i.e., a breast cancer that is estrogen receptor negative and progesterone receptor negative and HER2 negative), estrogen receptor/progesterone receptor (ER/PR) positive breast cancer, ER-positive breast cancer, or PR-positive breast cancer, or metastatic breast cancer. As used herein, "tumor" and "lesion" are used interchangeably.

The terms "resistant" and "refractory" refer to tumor cells that survive treatment with a therapeutic agent. Such cells may have responded to a therapeutic agent initially, but subsequently exhibited a reduction of responsiveness during treatment, or did not exhibit an adequate response to the therapeutic agent in that the cells continued to proliferate in the course of treatment with the agent. Examples of a resistant or refractory tumor is one where the treatment-free interval following completion of a course of therapy for a patient having the tumor is less than 6 months (*e.g.*, owing to recurrence of the cancer) or where there is tumor progression during the course of therapy.

FERAHEME (ferumoxytol) is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether. The overall colloidal particle size is

CSPC Exhibit 1026
Page 5 of 42

17-31 nm in diameter. The chemical formula of ferumoxytol is $Fe_{5874}O_{8752}C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa. An iron replacement product, ferumoxytol is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease.

FERAHEME is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD). The recommended dose of FERAHEME for this indication is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. In this context FERAHEME is administered as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec). The dosage is expressed in terms of mg of elemental iron, with each mL of FERAHEME containing 30 mg of elemental iron. The hematologic response (hemoglobin, ferritin, iron and transferrin saturation) should be evaluated at least one month following the second FERAHEME injection. The recommended FERAHEME dose may be re-administered to patients with persistent or recurrent iron deficiency anemia. For patients receiving hemodialysis, administer FERAHEME once the blood pressure is stable and the patient has completed at least one hour of hemodialysis. The patient is monitored for signs and symptoms of hypotension following each FERAHEME injection. FERAHEME is contraindicated in patients with evidence of iron overload, known hypersensitivity to FERAHEME or any of its components, and anemia not caused by iron deficiency.

Administration of FERAHEME may transiently affect the diagnostic ability of magnetic resonance (MR) imaging. Anticipated MR imaging studies should be conducted prior to the administration of FERAHEME. Alteration of MR imaging studies may persist for up to 3 months following the last FERAHEME dose. If MR imaging is required within 3 months after FERAHEME administration, T1- or proton density-weighted MR pulse sequences should be used to minimize the FERAHEME effects; MR imaging using T2-weighted pulse sequences should not be performed earlier than 4 weeks after the administration of FERAHEME. Maximum alteration of vascular MR imaging is anticipated to be evident for 1 – 2 days following FERAHEME administration. FERAHEME will not interfere with X-ray, computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), ultrasound or nuclear medicine imaging.

Although not an approved indication, ferumoxytol is currently being investigated as an imaging agent for the visualization of TAMs and tumor vasculature in cancer patients. Such imaging methods are disclosed, *e.g.*, in co-pending International Publication No. WO2014/113167.

CSPC Exhibit 1026
Page 6 of 42

II. Irinotecan sucrosofate liposome injection (MM-398)

MM-398 is a stable liposomal formulation of irinotecan sucrosofate (irinotecan sucrose octasulfate salt). MM-398 is typically provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of MM-398 may be diluted, *e.g.*, in 500 mL of 5% dextrose injection USP and infused over a 90 minute period. Additional information on the preparation and use of liposomal irinotecan sucrosofate can be found, *e.g.*, in United States patents 8,147,867 and 8,658,203, as well as in WIPO International Application No. PCT/US2013/045495.

An MM-398 liposome is a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules.

This stable liposomal formulation of irinotecan has several attributes designed to provide an improved therapeutic index. The controlled and sustained release improves activity by increasing duration of exposure of tumor tissue to irinotecan and SN-38. The long circulating pharmacokinetics of MM-398 and its high intravascular drug retention in the liposomes can promote an enhanced permeability and retention (EPR) effect. EPR is believed to promote deposition of liposomes at sites, such as malignant tumors, where the normal integrity of the vasculature (capillaries in particular) is compromised, resulting in leakage out of the capillary lumen of particulates such as liposomes. EPR may thus promote site-specific drug delivery of liposomes to solid tumors. EPR of MM-398 may result in a subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs), which metabolize irinotecan, converting it locally to the substantially more cytotoxic SN-38. This local bioactivation is believed to result in reduced drug exposure at potential sites of toxicity and increased exposure within the tumor.

III. Irinotecan glucuronidation

The enzyme produced by the UGT1A1 gene, UDP-glucuronosyltransferase 1, is responsible for bilirubin metabolism and also mediates SN-38 glucuronidation, which is the initial step in the predominant metabolic clearance pathway of this active metabolite of irinotecan. Besides its anti-tumor activity, SN-38 is also responsible for the severe toxicity sometimes associated with irinotecan therapy. Therefore, the glucuronidation of SN-38 to the inactive form, SN-38 glucuronide, is an important step in the modulation of irinotecan toxicity.

CSPC Exhibit 1026
Page 7 of 42

Mutational polymorphisms in the promoter of the UGT1A1 gene have been described in which there is a variable number of thymine adenine (ta) repeats. Promoters containing seven thymine adenine (ta) repeats (found in the UGT1A1*28 allele) have been found to be less active than the wild-type promoter (which has six repeats), resulting in reduced expression of UDP-glucuronosyltransferase 1. Patients who carry two deficient alleles of UGT1A1 exhibit reduced glucuronidation of SN-38.

The metabolic transformation of the irinotecan encapsulated in MM-398 to SN-38 includes two critical steps: (1) the release of the irinotecan from the liposome and (2) the conversion of free irinotecan to SN-38. The genetic polymorphisms in humans predictive for the toxicity of irinotecan and those of MM-398 can be considered similar. Nonetheless, due to the smaller tissue distribution, lower clearance and longer elimination half-life of SN-38 of the MM-398 formulation compared to free irinotecan, the deficient genetic polymorphisms may show more association with severe adverse events and/or efficacy.

IV. Administration

MM-398 is administered by intravenous (IV) infusion over 90 minutes at, *e.g.*, a dose of 80 mg/m^2 every two weeks in patients not carrying the UGT1A1*28 allele. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days. As used herein, the dose of MM-398 refers to the dose of irinotecan based on the molecular weight of irinotecan hydrochloride trihydrate unless clearly indicated otherwise.

The dose may also be expressed as the irinotecan free base. Converting a dose based on irinotecan hydrochloride trihydrate to a dose based on irinotecan free base is accomplished by multiplying the dose based on irinotecan hydrochloride trihydrate with the ratio of the molecular weight of irinotecan free base (586.68 g/mol) and the molecular weight of irinotecan hydrochloride trihydrate (677.19 g/mol). This ratio is 0.87 which can be used as a conversion factor. For example, the 80 mg/m^2 dose based on irinotecan hydrochloride trihydrate is equivalent to a 69.60 mg/m^2 dose based on irinotecan free base (80 x 0.87). In the clinic this is rounded to 70 mg/m^2 to minimize any potential dosing errors. Similarly, a 120 mg/m^2 dose of irinotecan hydrochloride trihydrate is equivalent to 100 mg/ m^2 of irinotecan free base.

V. Patient Populations

In one embodiment, a patient treated using the methods and compositions disclosed herein has exhibited evidence of recurrent or persistent breast cancer following primary chemotherapy.

In another embodiment, the patient has had and failed at least one prior platinum based chemotherapy regimen for management of primary or recurrent disease, *e.g.*, a chemotherapy regimen comprising carboplatin, cisplatin, or another organoplatinum compound.

In an additional embodiment, the patient has failed prior treatment with gemcitabine or become resistant to gemcitabine.

The compositions and methods disclosed herein are useful for the treatment of all breast cancers, including breast cancers that are refractory or resistant to other anti-cancer treatments.

VI. Outcomes

Provided herein are methods for treating breast cancer in a patient, comprising administering to the patient liposomal irinotecan (MM-398) according to a particular clinical dosage regimen.

Responses to therapy may include:

Pathologic complete response (pCR): absence of invasive cancer in the breast and lymph nodes following primary systemic treatment.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) which has reduction in short axis to <10 mm;

Partial Response (PR): At least a 30% decrease in the sum of dimensions of target lesions, taking as reference the baseline sum diameters;

Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study; or

Meanwhile, non-CR/Non-PD denotes a persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD) denotes at least a 20% increase in the sum of dimensions of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. The appearance of one or more new lesions is also considered progression;

In exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of a breast cancer.

In one embodiment the patient so treated exhibits pCR, CR, PR, or SD.

In another embodiment, the patient so treated experiences tumor shrinkage and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number

CSPC Exhibit 1026
Page 9 of 42

of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

In other embodiments, such improvement is measured by a reduction in the quantity and/or size of measurable lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter is to be recorded) as ≥10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or >20 mm by chest X-ray. The size of non-target sites comprising lesions, *e.g.*, pathological lymph nodes can also be measured for improvement. In one embodiment, lesions can be measured on chest x-rays or CT or MRI films.

In other embodiments, cytology or histology can be used to evaluate responsiveness to a therapy. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease can be considered to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

In some embodiments, administration of effective amounts of liposomal irinotecan according to any of the methods provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a breast tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, the provided methods of treatment produce a comparable clinical benefit rate (CBR = CR+ PR+ SD ≥ 6 months) better than that achieved by the same combinations of anti-cancer agents administered without concomitant MM-398 administration. In other embodiments, the improvement of clinical benefit rate is about 20% 20%, 30%, 40%, 50%, 60%, 70%, 80% or more compared to the same combinations of anti-cancer agents administered without concomitant MM-398 administration.

The following examples are illustrative and should not be construed as limiting the scope of this disclosure in any way; many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

EXAMPLES

Example 1: Treatment Protocols

A. Study Design

A clinical trial will enroll patients with metastatic breast cancer in 3 cohorts:

Cohort 1: ER-positive, and PR-positive, or ER/PR-positive breast cancer

CSPC Exhibit 1026
Page 10 of 42

Cohort 2: TNBC

Cohort 3: Breast cancer with active brain metastasis

There are five stages to this study:

1 Screening (-28 d): Patients undergo screening assessments to determine if they are eligible for the study.

2 Ferumoxytol (Day 1 – Day 2): patients receive ferumoxytol (FMX) infusion and undergo required MRI (Fe-MRI) scans and pre-treatment biopsy (if applicable, see Cohort requirements) prior to receiving MM-398.

3 MM-398 Treatment (C1D1 – progression of disease): Patients receive an MM-398 dose of 80 mg/m^2 every 2 weeks and other required assessments.

4 Follow up (+30 days 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/m^2 every two weeks and patients will be treated until disease progression or unacceptable toxicity.

5 Overall survival period: Overall survival (OS) will be collected every month once patients are off study.

B. Patient Selection and Discontinuation

Up to 30 evaluable patients will be enrolled in this study.

I. Inclusion Criteria: In order to be included in the study, patients must have/be:

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. 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 of less than 4.0 signals/cell.

• OR Negative by Dual-probe ISH defined as a HER2/CEP17 ratio of greater than 2.0 with an average HER2 copy number of fewer than 4.0 signals/cell.

CSPC Exhibit 1026
Page 11 of 42

ii. In addition, 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 below).

b) Documented metastatic disease with at least two radiologically measurable lesions as defined by RECIST v1.1 (Eur. J. Cancer 45 (2009) 228-247) (except Cohort 3, see inclusion criteria 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)

Expansion Phase additional inclusion criteria:

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 ≤ 3 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 (with the exception of Cohort 3)

CSPC Exhibit 1026
Page 12 of 42

The criteria for enrollment must be followed explicitly. Patients will be discontinued from the study treatment in the following circumstances:

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 v 1.1 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 the 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.

II. Exclusion Criteria: Patients must meet all the inclusion criteria listed above and none of the following 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)

b) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1

c) Have received irinotecan or bevacizumab (or other anti-VEGF therapy) therapy within the last six months; and for Expansion Phase patients, have received any prior treatment with a Topo1 inhibitor (irinotecan-derived or topotecan)

d) 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.

e) Unable to undergo MRI due to presence of errant metal, cardiac pacemakers, pain pumps or other MRI incompatible devices.

CSPC Exhibit 1026
Page 13 of 42

f) A history of allergic reactions to compounds similar to ferumoxytol, as described in full prescribing information for ferumoxytol injection, parenteral iron, dextran, iron-dextran, or parenteral iron-polysaccharide preparations

g) Known hypersensitivity to any of the components of MM-398, or other liposomal products

h) 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

i) Active infection or an unexplained fever greater than 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

j) Prior chemotherapy administered within three weeks, or within a time interval less than five half-lives of the agent, whichever is longer, prior to the first scheduled day of dosing in this study

k) Received radiation therapy in the last 14 days

l) Evidence of iron overload as determined by:

- Fasting transferrin saturation of >45 % and/or
- Serum ferritin levels >1000 ng /ml

m) Treated with iron supplements in the previous four weeks

n) HIV-positive patients on combination antiretroviral therapy or other conditions requiring treatment where there is a potential for ferumoxytol to have a negative pharmacokinetic interactions

o) Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, to cooperate, and to participate in the study, or to interfere with the interpretation of the results

p) 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.

CSPC Exhibit 1026
Page 14 of 42

C. 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.

D. Description and Use of MM-398

MM-398 is supplied as sterile, single-use vials containing 9.5 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 10 mL vial.

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.

MM-398 must be diluted prior to administration. The diluted solution is physically and chemically stable for 6 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 6 hours if kept at room temperature (15-30°C).

CSPC Exhibit 1026
Page 15 of 42

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.

Dosage and Administration

In one embodiment, MM-398 is dosed and administered as follows.

MM-398 will be administered by intravenous (IV) infusion over 90 minutes at a dose of 80 mg/m^2 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.

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 in-line filters or any diluents other than D5W. MM-398 can be administered at a rate of up to 1 mL/sec (30 mg/sec) using standard PVC-containing 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 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 they must discard unused portions of the product.

E. Important Treatment Considerations with MM-398

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.

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. Loss of fluids and electrolytes

CSPC Exhibit 1026
Page 16 of 42

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.

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, with discretion. Patients, who are known to have experienced Grade 3 or 4 neutropenia while receiving prior anti-neoplastic therapy, should be monitored carefully and managed.

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.

Colitis/Ileus

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

Thromboembolism

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

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.

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.

CSPC Exhibit 1026
Page 17 of 42

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.

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.

Other Toxicity Potential

MM-398, the new liposome 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.

F. Dose Modification Requirements

Dosing may be held for up to 2 weeks from an occurrence, to allow for recovery from toxicity related to the study treatments. 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 or its designee 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.

Infusion reactions will be monitored. Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as defined below:

CSPC Exhibit 1026
Page 18 of 42

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 25-50 mg IV

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), with discretion.

CSPC Exhibit 1026
Page 19 of 42

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.

G. MM-398 Dose Modifications for Hematological Toxicities

Prior to initiating a new cycle of therapy, the 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 1: MM-398 Dose Modifications for Neutrophil Count

Worst CTCAE Grade	ANC Levels (cells/mm^3)	Modification
Grade 1 or 2	1000 – 1999	Same as previous dose
Grade 3 or 4	<1000	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.

Table 2: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	Modification
< Grade 2	Same as previous dose
Grade 3 or 4	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.

H. MM-398 Dose Modifications for Non-Hematological 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 3: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	Description	Modification
Grade 1	2-3 stools/day > pretreatment	Same as previous dose
Grade 2	4-6 stools/day > pretreatment	Same as previous dose
Grade 3	7-9 stools/day > pretreatment	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.
Grade 4	>10 stools/day > pretreatment	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.

CSPC Exhibit 1026
Page 21 of 42

Table 4: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia

Worst Toxicity CTCAE Grade	Modification
Grade 1 or 2	Same as previous dose
Grade 3 or 4 (except nausea and vomiting)	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.
Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy and reduce dose to 60 mg/m^2; if the patient is already receiving, 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.

I. 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. 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.

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.

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

CSPC Exhibit 1026
Page 22 of 42

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.

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. Guidelines developed by an ASCO panel for treating chemotherapy-induced diarrhea are abstracted below.

Table 5: 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)

The synthetic octapeptide octreotide has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 micrograms twice daily to 500 micrograms three times daily, with a maximum tolerated dose of 2000 micrograms three times daily in a 5-day regimen. Patients should be advised to drink water copiously throughout treatment.

Other Treatments

Symptomatic treatment for other toxicities should be per institutional guidelines. Prevention of alopecia with cold cap or of stomatitis with iced mouth rinses is allowed.

CSPC Exhibit 1026
Page 23 of 42

I. 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. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. Refer to the country specific package inserts of 5-FU and leucovorin for any other drug interactions.

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; and
- Any other investigational therapy is not permitted.

J. Laboratory Procedures

Complete Blood Count

A complete blood count (CBC) will be performed locally, and must include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

Serum Chemistry

Serum chemistry panel will be performed centrally. Additionally, chemistry may also be assessed locally, and local lab results may be used for enrollment and treatment decisions, if central lab results are not available. If local lab results are used for enrollment, then local lab results must be used for all subsequent treatment decisions. Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.

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. Non-limiting examples of potential analyses include cytokine levels (*e.g.*, MCSF1 and IL-6), growth factors (*e.g.*, IGF-1 and EGFR family receptors and ligands), and enzyme levels (*e.g.*, MMP9).

Coagulation Profile

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

CSPC Exhibit 1026
Page 24 of 42

UGT1A1*28 Allele

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 (homozygous) for the UGT1A1*28 allele,

Urine or Serum Pregnancy Test

All women of child bearing potential must undergo a urine or serum pregnancy test.

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. The PK time points outlined in Table 13 below will be drawn during Cycles 1-3.

Table 6: Summary of PK Time-points in Treatment and Follow-up Phases

Sample	Time-point (Cycles 1-3)	Window
1	Immediately prior to MM-398 infusion on Day 1	-5 minutes
2	At the end of the MM-398 infusion	+5 minutes
3	+2 hours after the completion of the MM-398 infusion	+/- 30 minutes
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	----

K. Pain Assessment and Analgesic Consumption

Pain assessment and analgesic consumption diaries will be provided to the patients for recording their pain intensity daily on a visual analogue scale and to document their daily analgesic use.

L. EORTC-QLQ-C30

Quality of life will be assessed by the EORTC-QLQ-C30 instrument. The EORTC-QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included.

Patients will be required to complete the EORTC-QLQ-C30 questionnaire at time points outlined in the Schedule of Assessment. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients, for whom validated translations of the EORTC-QLQ-C30 questionnaire are available, will be required to complete the questionnaire.

M. Overall Survival/Post Study Follow-up

Overall survival data will be collected after a patient completes the 30 day follow-up visit, every 1 month (+/- 1 week) from the date of the 30 day follow-up visit. Post-discontinuation data to be collected will include: the date of disease progression (if not already documented; if patient discontinued from study treatment for reasons other than objective disease progression, patient should continue to undergo tumor assessment every 6 weeks, until commencement of new anti-neoplastic therapy or progressive disease); documentation of any anticancer treatment patient has received including the dates of any post-discontinuation systemic therapy, radiotherapy, or surgical intervention; and the date of death. All patients must be followed-up until death or study closure, whichever occurs first.

N. Determining the Severity and Relatedness of Adverse Events

Each adverse event will be graded according to the NCI CTCAE V 4.0, 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

The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study drug. This relationship should be described as related or non-related.

CSPC Exhibit 1026
Page 26 of 42

O. Efficacy Analyses

Progression Free Survival

PFS is defined as the number of months from the date of randomization to the date of death or progression, whichever occurred earlier (per RECIST 1.1). If neither death nor progression is observed during the study, PFS data will be censored at the last valid tumor assessment.

PFS will be compared between the treatment groups using paired un-stratified log-rank tests. The PFS curves will be estimated using Kaplan-Meier estimates. Estimates of the hazard ratios and corresponding 95% confidence intervals will be obtained using Cox proportional hazard models. Stratified analyses will also be carried out using the randomization stratification factors. Treatment effects adjusting for stratification variables and other prognostic covariates will be explored. In addition, different censoring and missing data imputing methods may be used to perform sensitivity analyses on PFS. Methodology for the sensitivity analyses will be fully specified in the Statistical Analysis Plan.
The analyses will be performed for ITT, PP and EP populations.

Time to Treatment Failure

Time to treatment failure is defined as time from randomization to either disease progression, death or study discontinuation due to toxicity. Kaplan-Meier analyses as specified for analyses of progression free survival will be performed for time to treatment failure. The analyses will be performed for ITT, PP and EP populations.

Objective Response Rate

The tumor assessment related to ORR will be determined using RECIST v1.1. If the Sponsor requires an independent review of the radiological assessments to support a new drug application or for any other reason, the response status of all patients may be reviewed by an independent panel of clinicians and may be reviewed by the Sponsor or its designee. In case of a discrepancy between the assessment of the independent panel and that of the investigator, the independent panel's assessment will take precedence.

Objective response rate (ORR) for each treatment group will be calculated combining the number of patients with a best overall response of confirmed CR or PR per RECIST v 1.1. The ORR is the best response recorded from randomization until progression or end of study. The number and percentage of patients experiencing objective response (confirmed CR + PR) at the time of analysis will be presented and the 95% confidence interval for the proportion will be calculated. Objective response rates from the treatment arms will be compared using pair-wise Fisher's Exact Tests. The analyses will be performed for ITT, PP and EP populations.

CSPC Exhibit 1026
Page 27 of 42

Tumor Marker Response Analysis

CA 19-9 serum levels will be measured within 7 days before the start of treatment (baseline), and subsequently every 6 weeks. Tumor marker response of CA19-9 will be evaluated by the change of CA19-9 serum levels. Response is defined as a decrease of 50% of CA 19-9 in relation to the baseline level at least once during the treatment period. Only patients with elevated baseline CA 19-9 value (> 30 U/mL) will be included in the calculation of tumor marker response rate.

Patient Reported Outcome Analyses

Analysis of the EORTC-QLQ-C30 questionnaires will be performed in accordance with the EORTC guidelines [22].

Safety Analysis

Treatment emergent adverse events will be presented by treatment arm, by patient, by NCI CTCAE grade and by MedDRA system organ class (SOC). Separate listings will be presented for total adverse events, serious adverse events, adverse events related to the study drugs and Grade 3 and 4 adverse events. Laboratory data will be presented by treatment arm and by visit. Abnormal laboratory values will be assessed according to NCI CTCAE grade, where possible. Evaluation of QTc will be done based upon Fridericia's correction method. CTCAE criteria will be applied to the QTc_F (i.e. Grade 3 = QTc > 500 msec). All the safety analyses will be performed by treatment arm, treatment cycle and week, where appropriate. Overall safety will also be evaluated by grade across cycles, SOC and extent of exposure. Additionally, safety analyses will include a comparison between the treatment arms in all patients in the Safety Population:

- Number of blood transfusions required
- Proportion of patients requiring G-CSF
- Adverse events resulting in dose delay or modification

Pharmacokinetics Analysis

Pharmacokinetic data will be collected on all patients randomized to either of the MM-398 arms. Plasma concentration-time data for MM-398 will be analyzed using population pharmacokinetic methods. Pharmacokinetic parameters will be estimated by Non-Linear Mixed Effects Modeling using NONMEM®, Version 7, Level 1.0 (ICON Development Solutions, Dublin, Ireland). PK parameters will include plasma C_{max}, T_{max}, AUC (area under the concentration curve), clearance, volume of distribution, and terminal elimination half-life. The effects of patient specific factors (age, race, gender, body weight, hepatic and renal function measures, ECOG value, etc.) on pharmacokinetic parameters will be evaluated. Population

CSPC Exhibit 1026
Page 28 of 42

PK/PD methods will be used to assess the relationships between drug exposure and efficacy and/or toxicity (*e.g.* neutropenia, diarrhea) parameters.

Additional exploratory analysis may be performed on the PK samples, to help clarify any safety, efficacy or PK issues related to MM-398 that arise during the course of the study. Concentration levels of 5-FU will be summarized descriptively.

Example 2: 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 Fe-MRI signal and TAMs, pharmacodynamic markers, or tumor response. Each patient will be required to complete their Fe-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 h Fe-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.

Table 7: Scan groups and required time points

Scan group	N[a]	Baseline	Baseline (repeat)	1-4 hours	24 hours	24 hours (repeat)	2 week 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

CSPC Exhibit 1026
Page 29 of 42

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 8: Fe-MRI schedule for Cohort 3 patients with active brain metastases:

Scan group	N	Baseline	Baseline (repeat)	1-4 hours	24 hours	24 hours (repeat)	2 week Baseline
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 hours: one brain scan and one body scan (body scan will capture the majority of the patient's extra-cranial disease).

b. Brain scan only will be completed at this time point

Administration of ferumoxytol (FERAHEME)

A single dose of ferumoxytol will be administered at Day 1 by intravenous infusion. Dosing is 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. Ferumoxytol has in the past been administered as an undiluted IV injection at a rate of up to 1 ml/sec (30 mg/second), with monitoring of vital signs. Alternatively, and in order to mitigate the risk of any toxicity associated with the bolus injection of ferumoxytol, all enrolled patients will receive a single dose of 5 mg/kg of ferumoxytol 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.

This dosing schedule is less intense than the approved label, which recommends two doses of 510 mg 3 to 8 days apart; however since the use of ferumoxytol as disclosed herein is as an imaging agent, as opposed to a replacement product for iron deficiency, a lower dose is more appropriate.

Ferumoxytol is administered while the patient is in a reclined or semi-reclined position. Patients are 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.

Important considerations when administering 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 $\geq$ 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

CSPC Exhibit 1026
Page 30 of 42

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 by an expert, is recommended.

Example 3: Physical, Chemical, and Pharmaceutical Properties of MM-398

Drug Product

The MM-398 drug product contains the drug substance irinotecan in the amount equivalent to 5 mg/mL of irinotecan hydrochloride trihydrate. The drug product liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as the sucrosofate salt. The liposome carriers are composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 6.81 mg/mL; cholesterol, 2.22 mg/mL; and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidylethanolamine (MPEG-2000-DSPE), 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer, 4.05 mg/mL; sodium chloride as isotonicity reagent, 8.42 mg/mL; and sucrose octasulfate as the drug trapping agent, 0.9 mg/mL. The solution is buffered at pH 7.25. In the vialed product, greater than 98% of the drug is encapsulated in the liposome carrier. MM-398 Injection is supplied as a sterile solution containing 5.0 mg/ml of irinotecan hydrochloride encapsulated in liposomes. The appearance of MM-398 is white to slightly yellow opaque liquid.

Description and List of Excipients

Table 14 below shows the composition of MM-398 Injection, 5.0 mg/ml drug product. Drug product composition for the 10 mL solution in the vial is also included.

Table 14: Quantitative Composition of MM-398 Injection, 5.0 mg/ml

Component	Concentration mg/mL	mg/vial (10 mL)
Irinotecan, hydrochloride, trihydrate	5.0	50
Distearoyl phosphatidylcholine (DSPC)	7.9	79
Cholesterol	2.6	26
Pegylated (MW: 2000) Distearoyl phosphatidylethanolamine (PEG 2000 DSPE)	0.14	1.4
Sodium chloride	7.9	79
N-2-Hydroxyethylpiperazine-N'-2- ethanesulfonic acid (HEPES)	4.8	48
Sodium hydroxide	q.s. to target pH to 6.5	q.s. to target pH to 6.5
Water for Injection	q.s. to 1.0 ml	q.s. to 10.0 ml

Abbreviations: MW = molecular weight; q.s. = add sufficient quantity.
Note: DSPC : Cholesterol : PEG 2000 DSPE = 3 : 2 : 0.015 (molar ratio)

Storage Conditions and Shelf Life

Prior to administration, MM-398 Injection must be diluted in 5% Dextrose Injection or Normal Saline (0.9% Sodium Chloride Injection) to a suitable volume for infusion. The solution for infusion (MM-398 Injection and its admixtures) must not be frozen. Freezing will disrupt the liposome structure and result in the release of free irinotecan. Because of the potential for microbial contamination during dilution, the solution for infusion should be used immediately, but may be stored at room temperature (15° to 30°C) for up to 4 hours prior to the start of the infusion. If necessary, the solution for infusion may be refrigerated (2° to 8°C) for no more than 24 hours prior to use. MM-398 has been tested for compatibility with limited materials, and no compatibility issues have been identified. The following materials were tested:

- Infusion sets (without in- line filter) made of PVC or polyethylene lined
- IV bags made of PVC or coextruded film of polyolefin/polyamide
- MM-398 drug product must be stored at 2°C to 8°C.

Adventitious Agents Safety Evaluation

The only component of biological origin in MM-398 is cholesterol, which is derived from sheep wool. Manufacture of MM-398 uses cholesterol exclusively derived from sheep in New Zealand, where BSE/TSE has not been reported. This material is in compliance with the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products {EMA/410/01 Rev. 3 - March 2011) adopted by the EU Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal products (CVMP). The MM-398 cGMP manufacturing process extensively controls for reduction and minimization of bioburden throughout and the drug product is sterile filtered prior to aseptic filling into vials. Product in-process and final testing assures sterility of MM 398.

Pharmacokinetics and Drug Metabolism in Humans

The pharmacokinetics of MM-398 was evaluated using sample-rich and sparse PK sampling across 6 studies (Study PEP0201, Study PEP0203, Study PEP0206, Study PIST-CRC-01, Study MM-398-01-01-02, and Study MM-398-07-03-01). Both non-compartmental analysis and population pharmacokinetic analysis were performed to evaluate the pharmacokinetic properties of MM-398.

CSPC Exhibit 1026
Page 32 of 42

Pharmacokinetic Parameters

A summary of PK parameters from non-compartmental analysis is provided in Table 2 below.

Table 2: Summary Statistics of MM-398 NCA Parameters across Multiple PK Studies

PK Parameters	Dose, mg/m^2	Analytes					
		Total Irinotecan			SN-38		
		N	Median	%IQR	N	Median	%IQR
C_{max} [μg/ml or ng/ml]‡	80	25	38.0	36	25	4.7	89
	120	45	59.4	41	45	7.2	57
$t_{1/2}$ [h]	80	23†	26.8	110	13†	49.3	103
	120	45	15.6	198	40†	57.4	67
$AUC_{0-\infty}$ [h·μg/ml or h·ng/ml]‡	80	23†	1030	169	13†	587	69
	120	45	1258	192	40†	574	64
V_d [L/m^2]	80	23†	2.2	55	NA	NA	NA
	120	45	1.9	52	NA	NA	NA

†$t_{1/2}$ and $AUC_{0-\infty}$ were not calculated for a subset of patients due to insufficient number of samples in the terminal phase. NA= not available. C_{max} are in μg/ml for total irinotecan and ng/ml for SN-38; AUC are in h μg/ml for total irinotecan and h ng/ml for SN-38.

Population Pharmacokinetics

Population pharmacokinetic analysis was performed for total irinotecan and SN-38 in 353 patients across 6 studies to identify major sources of inter-patient variability and to establish MM-398 exposure-response relationship. The SN-38 originating from the in vivo conversion of released irinotecan was predicted from the model and denoted as "SN-38 Converted".

From the population pharmacokinetic analysis, total irinotecan was approximately 3 orders of magnitude higher than SN-38. Compared to 120 mg/m^2 q3w, doses of 80 mg/m^2 q2w MM-398 resulted in similar average concentration, 1.5-fold lower C_{max} of both irinotecan and SN-38, and 7-fold higher SN-38 Converted C_{min}.

Endnotes

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known

CSPC Exhibit 1026
Page 33 of 42

or customary practice within the art to which the invention pertains and may be applied to the essential features set forth herein.

Those skilled in the art will recognize, or be able to ascertain and implement using no more than routine experimentation, many equivalents of the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims.

Any combinations of the embodiments disclosed in the various dependent claims are contemplated to be within the scope of the disclosure.

The disclosure of each and every U.S., international, or other patent or patent application or publication referred to hereinabove is incorporated herein by reference in its entirety.

CSPC Exhibit 1026
Page 34 of 42

What is claimed is:

1. A method of treatment of a breast cancer in a human patient, the method comprising: administering to the patient an effective amount of liposomal irinotecan, wherein the breast cancer is: a) HER2 negative metastatic breast cancer, or b) HER2 negative or HER2 positive and is metastatic breast cancer with at least one brain lesion.

2. The method of claim 1, wherein the administration is carried out in at least one cycle, wherein the cycle is a period of 2 weeks and the irinotecan is administered once per cycle on day 1 of each cycle, and wherein for at least a first cycle the liposomal irinotecan is administered at a dose of at least 60 mg/m^2 or at least 80 mg/m^2.

3. The method of claim 2, wherein for at least the first cycle the liposomal irinotecan is administered at a dose of 80, 100, 120, 150, 180, 210, or 240 mg/m^2.

4. The method of claim 2 or claim 3, wherein for at least the first cycle the liposomal irinotecan is administered at a dose of 80 mg/m^2.

5. The method of any one of claims 1-4 wherein the administration is carried out in at least two cycles and, if the patient is homozygous for the UGT1A1*28 allele, the dose following the first cycle is 20 mg/m^2 or 40 mg/m^2 lower than the dose given in the first cycle and if the patient is not homozygous for the UGT1A1*28 allele, the dose following the first cycle is the same as the dose given in the first cycle.

6. The method of any one of claims 1-5, wherein all administrations following the first cycle are at the same dose.

7. The method of any one of claims 1-6, wherein the breast cancer is triple negative or basal-like breast cancer.

8. The method of any one of claims 1-6, wherein the breast cancer is ER/PR positive breast cancer.

9. The method of any one of claims 1-8, wherein the breast cancer is HER2 negative metastatic breast cancer.

10. The method of any one of claims 1-8, wherein the breast cancer is HER2 negative or HER2 positive metastatic breast cancer with at least one brain lesion and wherein the at least one brain lesion is a progressive lesion.

CSPC Exhibit 1026
Page 35 of 42

11. The method of any one of claims 1-9, wherein the patient does not have any brain lesions and the breast cancer is HER2 0+ or 1+ by immunohistochemistry, HER2 negative by *in situ* hybridization, or HER2 negative by dual-probe *in situ* hybridization.

12. The method of any one of claims 1-11, wherein, prior to each administration of the liposomal irinotecan, the patient is pre-medicated with either or both of 1) dexamethasone and 2) either a 5-HT3 antagonist or another anti-emetic..

13. The method of any one of claims 1-12, wherein the liposomal irinotecan is administered intravenously over 90 minutes

14. The method of any one of claims 1-13, wherein, concomitant with the administration of the liposomal irinotecan, an effective amount of at least one anti-cancer agent other than irinotecan is co-administered to the patient.

15. The method of any one of claims 1-14, wherein the treatment results in a positive outcome in the patient.

16. The method of claim 15, wherein the positive outcome is pCR, CR, PR, or SD.

17. The method of claim 15, wherein the positive outcome is a reduction in: a) the number of cancer cells, b) tumor size, c) infiltration into peripheral organs, d) tumor metastasis or e) recurrence of tumor.

18. The method of any one of claims 1-17, wherein, prior to treatment with the liposomal irinotecan, the patient receives a ferumoxytol infusion followed by an MRI scan.

19. The method of any one of claims 1-17, wherein the liposomal irinotecan is MM-398.

20. A kit for treating a breast cancer in a human patient, the kit comprising a container holding 1) a second container holding at least one dose of liposomal irinotecan and 2) instructions for using the liposomal irinotecan according to the method of any one of claims 1-18.

21. The kit according to claim 20, wherein the liposomal irinotecan is MM-398.

CSPC Exhibit 1026
Page 36 of 42

AMENDED CLAIMS
received by the International Bureau on 13 May 2016 (13.05.2016)

What is claimed is:

1. Use of a single dose of 80 mg/m^2 of liposomal irinotecan administered once every two weeks for the treatment of breast cancer in a human patient following the administration of a dose of ferumoxytol to the human patient.

2. The method of claim 1, wherein the administration of the dose of ferumoxytol is followed by obtaining an image of the ferumoxytol in the patient prior to administration of the liposomal irinotecan and wherein the image is obtained with an MRI scan.

3. The method of claim 3, wherein the body areas scanned are determined by the location of the patient's lesion.

4. The use of claim 3, wherein the ferumoxytol is detected in a breast cancer lesion and the breast cancer lesion is selected from the group consisting of: a hormone receptor positive breast cancer lesion, an ER-positive lesion, a PR-positive lesion, a ER-positive/ PR-positive lesion, triple negative breast cancer lesion, a metastatic breast cancer lesion and an active brain metastatic lesion.

5. The use of anyone of claims 1-4, wherein the breast cancer lesion is a metastatic breast cancer lesion.

6 The use of claim 5, wherein the breast cancer lesion is an active brain metastatic lesion.

7. The use of any one of claims 1-6, wherein the human patient is not homozygous for the UGT1A1*28 allele.

8. The use of any one of claims 1-7, wherein the dose is a single dose of 5 mg/kg up to a total single dose that does not exceed 510 mg.

9. The use of anyone of claims 2-8, wherein the image is obtained 1-4 hours after the administration of the ferumoxytol.

10. The use of anyone of claims 2-8, wherein the image is obtained 24 hours after the administration of the ferumoxytol.

11. The use of any one of claims 1-10, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in a liposome.

STATEMENT UNDER ARTICLE 19(1)

Claims 1-21 have been canceled. The basis for new claims 1-11 is provided below.

(i) Basis for new claim 1: The basis for this claim can be found in original claim 4 and on page 10, lines 9-10, and page 15, lines 6-7, of the specification as filed.

(ii) Basis for new claim 2: The basis for this claim can be found page 10, lines 1-10, and claim 18, of the specification as filed.

(iii) Basis for new claim 3: The basis for this claim can be found on page 28, lines 17-18, of the specification as filed.

(iv) Basis for new claim 4: The basis for this claim can be found on page 11, lines 3-10, and the abstract of the specification as filed.

(v) Basis for new claim 5: The basis for this claim can be found on page 11, lines 9-10, of the specification as filed.

(vi) Basis for new claim 6: The basis for this claim can be found in Table 8 and on page 11, line9, of the specification as filed.

(vii) Basis for new claim 7: The basis for this claim can be found on page 7, lines 15-16, and in original claim 5, line 4 of the claim (as dependent from claim 4).

(ix) Basis for new claim 8: The basis for this claim can be found on page 29, lines 10-11.

(x) Basis for new claim 9: The basis for this claim can be found on page 28, tables 7 and 9, in the specification as originally filed.

(xi) Basis for new claim 10: The basis for this claim can be found on page 28, tables 7 and 8, in the specification as originally filed.

(xii) Basis for new claim 11: The basis for this claim can be found on page 1 line 32 through page 2, line 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/064491

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/436 A61K9/127 A61K35/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEFFREY R INFANTE ET AL: "Phase I and pharmacokinetic study of IHL-305 (PEGylated liposomal irinotecan) in patients with advanced solid tumors", CANCER CHEMOTHERAPY AND PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 70, no. 5, 2 September 2012 (2012-09-02), pages 699-705, XP035132528, ISSN: 1432-0843, DOI: 10.1007/S00280-012-1960-5	20
Y	page 702	1-21

X	WO 2014/113167 A1 (MERRIMACK PHARMACEUTICALS INC [US]) 24 July 2014 (2014-07-24)	20,21
Y	claim 15	1-21

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 February 2016	19/02/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Steendijk, Martin

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/064491

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/030864 A1 (NEOPHARM INC [US]; RAHMAN AQUILUR [US]; AHMAD IMRAN [US]) 17 April 2003 (2003-04-17)	20,21
Y	page 6; claim 1	1-21

X	US 2007/110798 A1 (DRUMMOND DARYL C [US] ET AL) 17 May 2007 (2007-05-17)	20,21
Y	page 25; claims; example 10	1-21

Y	HIDETOSHI HAYASHI ET AL: "Phase II study of bi-weekly irinotecan for patients with previously treated HER2-negative metastatic breast cancer: KMBOG0610B", BREAST CANCER, vol. 20, no. 2, 29 November 2011 (2011-11-29), pages 131-136, XP055246819, JP ISSN: 1340-6868, DOI: 10.1007/s12282-011-0316-z abstract	1-21

Y	WO 2012/012454 A1 (BIPAR SCIENCES INC [US]; BRADLEY CHARLES [US]) 26 January 2012 (2012-01-26) claims	1-21

A	WO 2013/188586 A1 (MERRIMACK PHARMACEUTICALS INC [US]) 19 December 2013 (2013-12-19) claims	1-21

X,P	Anonymous: "Abstract P5-01-06: Characterization of metastatic breast cancer lesions with ferumoxytol MRI and treatment response to MM-398, nanoliposomal irinotecan (nal-IRI)", , 1 May 2015 (2015-05-01), XP55245815, Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/75/9_Supplement/P5-01-06 [retrieved on 2016-01-28] abstract	1-21

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/064491

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014113167 A1	24-07-2014	AU 2013374248 A1	11-06-2015
		US 2014170075 A1	19-06-2014
		WO 2014113167 A1	24-07-2014
WO 03030864 A1	17-04-2003	US 2005019387 A1	27-01-2005
		WO 03030864 A1	17-04-2003
US 2007110798 A1	17-05-2007	US 2007110798 A1	17-05-2007
		US 2014127136 A1	08-05-2014
WO 2012012454 A1	26-01-2012	AU 2011282223 A1	07-03-2013
		CA 2805774 A1	26-01-2012
		EP 2595618 A1	29-05-2013
		EP 2595619 A1	29-05-2013
		JP 2013531068 A	01-08-2013
		JP 2013531069 A	01-08-2013
		US 2013274281 A1	17-10-2013
		WO 2012012448 A1	26-01-2012
		WO 2012012454 A1	26-01-2012
WO 2013188586 A1	19-12-2013	AU 2013202947 A1	16-01-2014
		AU 2013274287 A1	29-01-2015
		CA 2875824 A1	19-12-2013
		CN 104717961 A	17-06-2015
		EP 2861210 A1	22-04-2015
		JP 2015523355 A	13-08-2015
		KR 20150021565 A	02-03-2015
		US 2015182521 A1	02-07-2015
		US 2015328156 A1	19-11-2015
		US 2015374682 A1	31-12-2015
		WO 2013188586 A1	19-12-2013