Statistical Analysis Plan

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

PROTOCOL VERSION AND DATE: VERSION 6.0 – 03 APRIL 2017

SAP Version	Date
Final Version 1.0	30 October 2018
Final Version 1.1	28 February 2019

STUDY NUMBER:	MM-398-01-01-02
EudraCT number:	2014-003673-42
PROTOCOL TITLE:	**A PHASE 1 STUDY IN PATIENTS TREATED WITH MM-398 (NANOLIPOSOMAL IRINOTECAN, NAL-IRI) TO DETERMINE TUMOR DRUG LEVELS AND TO EVALUATE THE FEASIBILITY OF FERUMOXYTOL MAGNETIC RESONANCE IMAGING TO MEASURE TUMOR ASSOCIATED MACROPHAGES AND TO PREDICT PATIENT RESPONSE TO TREATMENT** **(PROTOCOL V 6.0)**
SAP VERSION:	Version 1.1
SAP DATE:	28 February 2019

Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Clinical Statistics Designee	PPD Adjoint PPD Ipsen Innovation SAS		
Medical Development	PPD PPD Oncology Ipsen Bioscience, Inc.		

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Biostatistics Lead	PPD Associate Director, Ipsen Bioscience, Inc. 650 East Kendall Street Cambridge, MA 02142		

Biostatistics Reviewer	PPD Senior Biostatistician Ipsen Bioscience, Inc. 650 East Kendall Street Cambridge, MA 02142)		

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
24	11.3.2	Secondary efficacy analysis will be based on Investigator determined tumor response assessment following RECIST 1.1. Cohort 3 CNS disease will be analyzed according to RECIST and modified RECIST, separately.	Secondary efficacy analysis will be based on Investigator determined tumor response assessment following RECIST 1.1. Cohort 3 CNS disease will be analyzed according to RECIST and modified RECIST, separately. The worst case between RECIST and modified RECIST may be reported.	Worst case scenario was added.
26	11.3.2.1	N/A	As a sensitivity analysis, PFS will also be analyzed following the same censoring rule in table 3 with 16 weeks of baseline or the last non-PD/non-NE tumor assessment time window being applied.	16 weeks censoring rule was added as a sensitivity analysis.

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BC	Breast cancer
BUN	Blood urea nitrogen
CES	Carboxylesterase
CL	Clearance
Cmax	Maximum concentration
CNS	Central nervous system
CRC	Colorectal cancer
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DOR	Duration of objective response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ER	Estrogen Receptor
FMX-MRI	Ferumoxytol magnetic resonance imaging
FMX	Ferumoxytol
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liter
mg	Milligram
MRI	Magnetic resonance imaging
ng	Nanogram
nm	Nanometer
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamic; or Progressive disease
PET	Positron emission tomography
PK	Pharmacokinetic
PI	Principal investigator
PR	Progesterone Receptor or Partial response
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
t1/2	Half-life
TAM	Tumor associated macrophages
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
WBC	White blood count

1 OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol MM-398-01-01-02: A phase 1 study in patients treated with MM-398 (Nanoliposomal Irinotecan, nal-IRI) to determine tumor drug levels and to evaluate the feasibility of ferumoxytol magnetic resonance imaging to measure tumor associated macrophages (TAMs) and to predict patient response to treatment.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E9): Guidance on Statistical Principles in Clinical Trials (US FDA, 1998).

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol MM-398-01-01-02, Version 6.0 dated 03 APRIL 2017
- Subject case report forms (CRFs) for Protocol MM-398-01-01-02 V6.0
- ICH Guidance on Statistical Principles for Clinical Trials (US FDA, 1998)
- FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA, 2007).

The reader of this SAP is also encouraged to read the clinical protocols for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol MM-398-01-01-02 V6.0. Additional post-hoc analyses may be performed to better understand the observed results.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

Pilot Phase (Completed)

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

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

Expansion Phase:

In patients with locally advanced or metastatic breast cancer:

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

2.2 Secondary Objectives

All Phases:

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

Pilot Phase (Completed):

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

Expansion Phase:

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

2.3 Exploratory Objectives

Pilot Phase (Completed):

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

Expansion Phase:

- To evaluate a set of potential biomarkers from tumor tissue and blood samples for their ability to predict PK and/or response to MM-398 treatment
  Exploratory analyses will be performed ad-hoc only. When applicable, detailed analyses and results will be documented separately.

3 STUDY DESIGN

3.1 General Design and Plan

This study comprises two phases: pilot phase and expansion phase.

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

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

The Expansion Phase will enroll cohorts of single indications of patients with locally advanced or metastatic breast cancer in 3 cohorts of 10 patients each depending on sub-type of breast cancer:

Cohort 1: ER and/or PR-positive breast cancer
Cohort 2: Triple negative breast cancer (TNBC)
Cohort 3: Breast Cancer (BC) with active brain metastasis

There are four stages to each phase of this study:

- Screening (-28d): patients undergo screening assessments to determine if they are eligible for the study
- Ferumoxytol (FMX) (Day 1 Day 2)**:** patients receive ferumoxytol infusion and undergo required FMX-MRI scans and pre-treatment biopsy (if applicable, see Cohort requirements) prior to receiving MM-398
- MM-398 Treatment (C1D1 progression of disease): patients receive an MM-398 dose of 60 mg/m^2 every 2 weeks, which should be dose escalated to 80 mg/m^2 every 2 weeks in subsequent doses depending on patient tolerance, other required assessments, and undergo a post-treatment (MM-398) multiple pass core biopsy
- Follow up (+30d from last dose): patients return to clinic 30 days after their last dose of MM-398 for final safety assessments

Ferumoxytol magnetic resonance imaging (FMX-MRI) will be done for both pilot phase and expansion phase. The schedule for pilot phase FMX-MRI is: pre-dose of ferumoxytol, 1-4 hours post dose and 24 hours post dose of ferumoxytol.

The schedule for expansion phase is outlined in Tables 1 and 2:

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

Scan group	N[a]	Baseline	Baseline (repeat)	1-4 h	24 h	24 h (repeat)	2 wk Baseline
1	5	X	X		X		X
2	5	X		X	X	X	
3	10	X		X	X		

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

For patients with active brain metastases enrolled into Cohort 3, the following FMX-MRI schedule will be followed:

Table 2 Expansion Phase Cohort 3 MRI Scan Time Points

Scan group	N	Baseline	Baseline (repeat)	1-4 h	24 h	24 h (repeat)	2 wk 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 h: one brain scan and one body scan (body scan will capture the majority of the patient's extra-cranial disease; see imaging manual for details)
b. Brain scan only will be completed at this time point

A single dose of ferumoxytol will be administered at Day 1 by intravenous injection at a rate of up to 1 ml/sec (30 mg/second), with monitoring of vital signs. MM-398 will be administered by intravenous (IV) infusion over 90 minutes starting at a dose of 60 mg/m^2 every two weeks. The MM-398 period (C1D1) should begin within 7 days of the ferumoxytol infusion. The dose of MM-398 should be escalated to 80 mg/m^2 every two weeks depending on patient tolerance. Patients will be treated until disease progression or unacceptable toxicity.

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

3.2 Treatment Assignment

All patients will be administered a single dose 5 mg/kg of ferumoxytol at Day 1 by intravenous infusion as an imaging agent. MM-398 will be administered at a dose of 60 mg/m^2 every two weeks starting at Cycle 1 Day 1 during MM-398 treatment phase.

3.3 Treatment Blinding

This is an open-labeled single treatment arm study. There is no treatment blinding.

4 SAMPLE SIZE DETERMINATION

No formal hypothesis testing is performed for this study. Therefore, the Pilot and Expansion Phases are not powered to detect statistical differences on any parameters. Results will be descriptive.

The Pilot Phase will enroll 12 to 20 patients with various indications, while the Expansion Phase will enroll approximately 30 metastatic breast cancer patients across three cohorts.

The Expansion Phase ORR is estimated to be around 29% with a 95% confidence interval (14.6-46.3) [Awada, 2013]. Other studies showed similar response rates ranges ranging from 5-32% [Kümler, 2013]. Hypothesizing a true ORR of 30%, the probability of at least 14 responses of 30 evaluable patients would be 0.04. The probability of at least 13 responses would be 0.084.

5 SEQUENCE OF PLANNED ANALYSES

5.1 Interim Analyses

No interim analysis will be performed. Data may be analyzed while study is ongoing for administrative purposes.

5.2 Final Analyses

No formal hypothesis testing will be performed in the Pilot or Expansion Phases of this study. Descriptive statistics will be calculated to summarize categorical and continuous parameters. Parameters will be reported by study phase (pilot and expansion phase) and expansion phase will be further summarized by each cohort and total. When appropriate, the Pilot and Expansion study phases may be pooled. The final analysis will be conducted when the last patient enrolled in expansion phase discontinued study treatment for any reason or after the patient has been treated for six months, whichever comes first. A single cut-off date will be applied wherein all data for all patients up to that date will be included in the analysis and all data reported after the cut-off date will be excluded from analysis.

Exploratory analyses and/or post-hoc analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices and/or addendum to the CSR.

Subsequent analyses of the data may be generated as needed per regulatory obligation.

6 ANALYSIS POPULATIONS

- **Screened population:** This population includes all patients screened (i.e. who signed the informed consent).
- **Safety population:** This population includes all patients receiving at least one dose of MM-398 or ferumoxytol. If ferumoxytol safety population is different from MM-398 safety population, safety analysis will be performed separately on both populations.

Depending upon patients receiving MM-398 and not ferumoxytol and vice versa, the safety population may be expanded in order to not dilute any adverse event rate:
  - Ferumoxytol safety population: any patient receiving ferumoxytol. All analyses using this population will be based on the treatment actually received.
  - MM-398 safety population: all patient receiving at least one dose of MM-398. All analysis using this population will be based on the treatment actually received.
- **Efficacy evaluable population**: This population includes all patients receiving at least one dose of MM-398. All statistical analyses of data on non-imaging related efficacy analyses will be performed using efficacy evaluable population.
- **Pharmacodynamic (PD) evaluable population**: This population includes all efficacy evaluable patients with the following: a) pre-treatment FMX-MRI scan(s) and b) radiological scans at 8 weeks. All statistical analyses of data on imaging related efficacy analyses will be performed using PD evaluable population.
- **Pharmacokinetic (PK) population**: This population includes patients receiving at least one dose of MM-398, and blood samples at the predefined timepoints adequately collected (with no major protocol deviations affecting the PK variables & with sufficient number of plasma concentrations to estimate the main PK parameters (Cmax, AUC)). PK analysis will be documented in a separate SAP.

The term 'All Screened Patients' will be used to describe the set of all patients who signed informed consent, including patients who failed screening and any others who initiated screening.

7 GENERAL STATISTICAL METHODS

7.1 General Methodology

Categorical/qualitative data will be summarized using the number of non-missing observations, frequency counts and percentages. All percentages will be presented as one-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

For continuous variables, descriptive statistics will include the number of non-missing observations (n), mean, standard deviation, median, minimum and maximum. Missing data will be counted but not included in percentage calculations. Where applicable, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and standard deviation.

Unless otherwise specified, patients will be counted only once in each tabular summary (e.g. each parameter & visit combination). Reported data that are excluded from tables, e.g. patients excluded from the corresponding analysis population or extraneous measurements (e.g. repeat assessments), will be included in the patient listings.

The pre-treatment period is the time from informed consent to the date of first study drug administration of ferumoxytol or MM-398 respectively. On-treatment period for ferumoxytol is defined as time from ferumoxytol treatment administration to prior to MM-398 administration or within 30 days from date of ferumoxytol termination if patient didn't receive MM-398. The on-treatment period for MM-398 is defined as time from the first administration of MM-398 to 30

days after date of MM-398 termination. Observations recorded on the same date of the first administration of study drug will be considered as on-treatment, unless otherwise indicated by collection time. The post-treatment period is the time following 30 days after the last administration of study drug.

In general, the patient listings will be sorted by phase, patient number and assessment date (and time) if applicable.

For patients who received study drug the reference start date (RFSTDT) is the date of MM-398 administration. Study day is computed as:

- (event/visit date RFSTDT), if event/visit date < RFSTDT
- (event/visit date RFSTDT+1), if event/visit date ≥ RFSTDT.

Tables, figures, and listings (TFLs) including intext TFLs as described in this document and in the mock shells, will be created using SAS version 9.4 or higher. Mock table, listing, and figure shells will be developed for detailed information on the layout.

7.2 Methods for Missing Data, Multiple Observations, and Outliers

7.2.1 General Considerations

In general, data will be analyzed as received from the clinical database. Hence, missing measurements including those caused by dropouts will not be imputed.

7.2.2 Partial and Missing Dates

Missing or partially missing date in the following situations will be imputed for purposes of analysis.

Partial Dates for Death: It is anticipated that nearly all death dates will be completely captured. Any partially missing date of this type will be queried before statistical analyses are performed. In cases of partial dates, death date may be known to month and year. For the primary analysis, date recorded as month and year only will be imputed to the later date of: 1st of the corresponding month and last known alive date plus one day.

Partial/Missing Dates for Study-Related Visits or Procedures: It is anticipated that all study-related visit and procedure dates entered into the clinical study database will be complete (i.e. day, month, year are all recorded) and accurate. Any missing or partially missing date of this type will be queried before statistical analyses are performed. If the day, month, or year is still unknown, then the dates will be imputed as follows for purposes of analysis:

- If the day of the visit or procedure date is missing, then take the previous visit and add the number of days to the next visit according to the visit schedule.
- If the month of the visit or procedure date is missing, then take the previous visit and add the number of months to the next visit according to the visit schedule.
- If the year of the visit or procedure date is missing, then the year will be queried. If the year is unknown, no imputation of year will take place.

Partial/Missing Start Date for Adverse Events or concomitant medications: Missing adverse event (AE) dates will be imputed for the purpose of classification as treatment emergent or not. For any adverse event or concomitant medication that has a missing or incomplete start date, a query will be issued to capture the full date. If only a partial date is reported for the start of an AE or medication, a complete date will be estimated using the following algorithm:

- Completely missing (i.e., missing the year, month and day): the date of first study drug administration. Therefore, any such AE would be treatment emergent, and any such medication would be concomitant.
- Only the year is reported (i.e., missing the month and day): earlier date of '1 January' and the date of first study drug administration.
- The year and month are reported (i.e., missing the day): earlier date of first day of the month and the date of first study drug administration.

Partial/Missing End Date for Adverse Events or concomitant medications: If only a partial date is reported for the end of an AE or medication, a complete date will be estimated:

- Completely missing: then the AE or medication will be considered ongoing at the end of the study.
- Only the year is reported: '31 December' will be used, unless this is after the date of final follow-up, in which case the AE or medication will be considered ongoing at the end of the study.
- The year and month are reported: the last day of the month will be used, unless this is after the date of final follow-up, in which case the AE or medication will be considered ongoing at the end of the study.

Partial/Missing start date of post study drug anticancer therapies: If only a partial date is reported for the start date of post study drug anticancer therapies, a complete date will be estimated:

- Completely missing (i.e., missing the year, month and day): the date of last study drug administration+1.
- Only the year is reported: later date of '1 January' and the date of last study drug administration+1.
- The year and month are reported: later date of first day of the month and the date of last study drug administration +1.

7.3 Multicenter Studies

No by-center displays or adjustments for center are planned for this study.

7.4 Multiple Comparisons and Multiplicity

No testing will be performed in this study.

7.5 Planned Subgroups, Interactions, and Covariates

No subgroup analysis is planned.

7.6 Definitions and General Terminology

7.6.1 Baseline

- **Baseline for Ferumoxytol Safety Period**

Baseline for the ferumoxytol period is the last observation before the administration of ferumoxytol.

- **Baseline for MM-398 Safety Period**

Baseline for the MM-398 safety period is the last observation before the first administration of MM-398.

7.6.2 Protocol Deviations

Important Protocol Deviations (IPDs) will be identified and documented for all patients in the safety population prior to database lock based on a review of patient data by sponsor.

The potentially important protocol deviations to be reviewed include, but are not limited to patients who:

1. Receipt of any prohibited therapies as defined in Section 6.5 of the protocol
2. Inclusion/exclusion criteria deviations, unless a waiver was granted
3. Significant deviations in study drug administration

All IPDs will be listed by patient. The number and percentage of patients with IPDs will be summarized by type of deviation and by cohort.

7.6.3 Study Periods

For the evaluation of safety, assessments will be assigned to study periods. These will be:

- Ferumoxytol safety period: from time of the first dose of ferumoxytol to the time of the first dose of MM-398. If an observation contains a date only, then the corresponding ferumoxytol safety period is the time from the date of the first dose of ferumoxytol to the day before the date of the first administration of MM-398. If the patient does not receive MM-398, the ferumoxytol safety period ends at 30 days after the date of the ferumoxytol dose.
- MM-398 safety period: from time of the first dose of MM-398 to 30 days after the date of the last study drug administration of MM-398. If an observation contains a date only, then the corresponding MM-398 safety period begins on the date of the first administration of MM-398.
- Events/observations will be assigned to study periods based on the start date or date and time if time is available.

7.6.4 Derived and Computed Variables

7.6.4.1 General

When applicable, below derivation rules should be followed:

Time in months: the following will be used to compute time from date 1 to date 2 in months, which will be presented to one decimal place:

time in months =(date2-date1+1)/(365.25/12);

Age: the number of years since birth to date of informed consent. In SAS, this is computed as:

age = floor((intck('month',birthdate,ICdate)- (day(ICdate) < day(birthdate))) / 12);

Body temperature in °C: body temperature will be presented in Celsius to one decimal place. Conversion from Fahrenheit is:

temperature in °C = ([temperature in °F]-32)(5/9);*

Weight in kg: weight will be presented in kilograms to one decimal place. Conversion from pounds is:

weight in kg =0.4536{weight in lb};*

Height in cm: height will be presented in whole centimeters. Conversion from inches is:

height in cm =2.54{height in inches};*

BMI: body mass index in kg/m^2, presented to one decimal place:

BMI ={weight in kg}/{height in cm/100}^{2};

Time since cytological/histo-pathological diagnosis: time from date of first cytological or histo-pathological diagnosis to the date of informed consent in months.

Time since last anticancer therapy: time from date of last dose of most recent prior anticancer therapy to the date of informed consent in months. For example, if PAENDTC is the variable for prior anticancer last dose date:

time since last treatment ={max(PAENDTC)-date of informed consent};

Time since metastatic diagnosis: time from date of first metastatic diagnosis to the date of informed consent in months.

Time on treatment MM-398: number of days from first treatment to last treatment:

{date of last MM-398 dose} - {date of first MM-398 dose}+1;

Dose intensity (mg/m^2/week):

*{cumulative actual dose in mg/m^2}*7/ {days of exposure}*

where days of exposure for MM-398: (date of last study drug administration + 14 date of first study drug administration)

8 STUDY SUBJECTS

Patient disposition for expansion Phase will be summarized by each cohort and total. The total number of all screened patients will be used and presented in the column header and serves as the denominator for calculating percentage. Following will be presented in the disposition table:

- The number and percentage of patients enrolled
- The number and percentage of patients screened failures
- Reasons for screen failures
- The number and percentage of patients dosed with ferumoxytol (Ferumoxytol Safety Population)
- The number and percentage of patients dosed with MM-398 (MM-398 Safety Populations)

In addition, patient disposition will be summarized using safety population:

- The number and percentage of patients included in Efficacy Evaluable Population
- The number and percentage of patients included in PD population
- The number and percentage of patients discontinued from treatment early by reasons for discontinuation
- The number and percentage of patients discontinued from study (i.e. did not complete study to 30-day follow-up) early by reasons for discontinuation.

8.1 Protocol Deviations

Prior to database lock, Important Protocol Deviations (IPDs) will be identified through programmatic checks of study data, as well as through review of selected data listings. The potential IPDs to be reviewed include, but are not limited to, patients who:

- Did not meet key inclusion/exclusion criteria
- Received any disallowed concomitant medication during the treatment period
- Other

Individual IPDs will be presented in a data listing. The number and percentage of patients with IPDs will be summarized by study phases and overall.

8.2 Inclusion and Exclusion Criteria

Violations of key inclusion and exclusion criterion will be included in protocol violation tabulations. Inclusion criteria will be listed for non-screen failures who did not meet criteria. Exclusion criteria will be listed for non-screen failures who met criteria.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline data will be presented by Pilot and Expansion Phases, where patients in expansion phases will be summarized by each cohort and total. No formal statistical analysis will be performed on these data.

Summaries will be created for the following patient characteristics:

- Patient demographics (each analysis population)
- Baseline disease characteristics (each analysis population)
- Prior therapies (each analysis population)
- Medical history and pre-existing conditions (MM-398 safety population)
- Concomitant therapies (MM-398 safety population)

9.1 Demographics

A summary of the number and percentage of patients in each category for gender, race and ethnicity will be presented. Age (years), height (cm), weight (kg), body mass index (BMI) and body mass index group will be summarized using summary statistics for continuous variables.

9.2 Baseline Characteristics

The following baseline characteristics will be summarized, where applicable, by study phases and cohorts within expansion phase:

- ECOG Status
- UGT1A1*28 allele (Homozygous 7/7, non-Homozygous)
- Cancer site
- Status of brain metastases
- Time since histo-pathological diagnosis
- Stage at diagnosis
- Time since metastatic diagnosis

9.3 Prior Anti-Cancer Therapy, Radiotherapy, and Surgery

The following prior anticancer therapy (related to study indication) characteristics will be tabulated by study phases and cohorts within expansion phase:

- Type of prior anti-cancer therapy
- Administration setting
- Number of prior anti-cancer regimens

Time since last anti-cancer therapy prior to study enrollment will be summarized.

Prior radiotherapies and prior surgeries related to study indication will be tabulated, with further tabulation by location and by reason for treatment/procedure.

9.4 Medical History and Pre-existing Conditions

Patient medical history will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 17 or higher. Prior medical history will be tabulated.

9.5 Prior and Concomitant Therapies

Summaries of all medications taken during the course of the study will be recorded. Medications will be standardized based on the World Health Organization Drug Classification Dictionary

(WHODRUG, version 01DEC2017 WHODDE) Anatomic Therapeutic Class (ATC) Level II preferred term.

All medications (excluding study drug) taken during the course of the study with a start date or an end date on or after the date of the first dose of MM-398, or marked as ongoing will be considered concomitant. Medications stopped prior to the date of the first dose of study drug will be considered as prior medication. Prior medications will be flagged on the concomitant medication listing.

The number and percent of patients taking medications will be summarized by study period and WHODRUG ATC Level II and preferred term. In the tabular presentation, medications will be sorted by frequency and then alphabetically by preferred term. If a patient has more than one qualifying record for a medication, the patient will be counted only once in the tabulation.

9.6 Concomitant Procedures

Concomitant procedures will be presented in a listing which will include the procedure term (verbatim), date, indication (reason for the procedure), yes/no indicator of relationship to an adverse event, and findings from the procedure.

10 TREATMENT COMPLIANCE AND EXPOSURE

Treatment exposure will be summarized separately for ferumoxytol and MM-398. Exposure to ferumoxytol will be summarized by the amount of drug administered, both as mg/kg and total mg.

The following MM-398 exposure metrics will be summarized by cycle:

- summary statistics for the amount of drug administered, in mg/m^2
- summary statistics for the amount of drug administered, in mg
- number of patients with dose delay
- number of patients with dose reduction.

Overall exposure of MM-398 will be summarized by:

- frequency table of the total number cycles of doses administered
- summary statistics for treatment duration in weeks
- cumulative dose received, in mg/m^2
- cumulative dose received, in mg
- dose intensity, in $mg/m^2/wk$

11 EFFICACY ANALYSES

11.1 Primary Efficacy Endpoints:

The efficacy endpoints will be summarized for efficacy evaluable population and PD evaluable population by using descriptive statistics.

Pilot Phase:

- **Feasibility of FMX-MRI on identifying tumor associated macrophages (TAMs):**

FMX-MRI will be conducted on day 1 before and 1-4 h after intravenous ferumoxytol (FMX) administration, then after 24 h and/or 72 h. For the quality scan of FMX-MRI, scanner type (i.e. 1.5T), impact of scan quality on analysis (i.e. adequate for evaluation, suboptimal but completed for evaluation, or inadequate for evaluation), reasons for scan suboptimal/inadequate) and scan location (i.e. Body) will be assessed.

- **Tumor Levels of Irinotecan and SN-38:**

During pilot phase, two biopsies are collected on Day 4 of the ferumoxytol phase and two biopsies are collected three days after the first dose of MM-398. Tumor levels of irinotecan and SN-38 in core biopsy will be measured after MM-398 dosing.

Expansion Phase:

- **Feasibility of Ferumoxytol (FMX) Quantitation in Tumor Lesion**

Feasibility of ferumoxytol (FMX) quantitation in tumor lesion is also assessed through the acquisition of baseline and follow-up images of sufficient quality that enable quantitative analysis to be performed.

Eligible patients should have serial FMX-MRI scans prior to and following FMX infusion as determined by their scan group. After MRI acquisition, the R2* signal is used to calculate FMX levels in plasma, tumor lesions and reference tissue by comparison to a phantom-based standard curve.

- **The Relationship Between Ferumoxytol (FMX) tumor uptake and tumor response to MM-398**

FMX-MRI will be done for various tissues and at different timepoints. Corrected FMX uptake (post-baseline value baseline value) will be recorded by each time point and tissues. Ferumoxytol uptakes will be associated with change in tumor lesion size.

11.2 Primary Efficacy Analysis:

Pilot Phase

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

- To evaluate the feasibility of delayed ferumoxytol MRI (FMX-MRI) to identify tumor associated macrophages (TAMs)
  The quality of FMX-MRI scan on impact of evaluation will be summarized descriptively by evaluation time points. For the quality scan of FMX-MRI, number of FMX-MRI scans obtained, number of scans accepted for evaluation, and scan location (i.e. Body) at each time point will be assessed. If there is more than one image data at the same timepoint for a patient, image data are averaged first before summarizing.

- To measure tumor levels of irinotecan and SN-38
  Tumor levels of irinotecan and SN-38 during Pilot phase were assessed through tumor tissue biopsy. The data are summarized using descriptive statistics with n, min, max, mean 25th percentiles (Q1), 75th percentiles (Q3) and median per lesion. Tumor levels of irinotecan and SN-38 in core biopsy are reported in Merrimack Pharmaceuticals Synopsis Clinical Study Report MM-398-01-01-02, published on 18-Dec-2014 (Appendix X). No further analysis is required.

Expansion Phase

In patients with locally advanced or metastatic breast cancer:

- To further investigate the feasibility of ferumoxytol (FMX) quantitation in tumor lesions

  Feasibility of ferumoxytol (FMX) quantitation in tumor lesion is assessed through the acquisition of baseline and follow-up images of sufficient quality that enable quantitative analysis to be performed. Sufficient quality is assessed by summarizing images that are adequate for evaluation, suboptimal but completed for evaluation, or inadequate for evaluation at each visit.

- To characterize the relationship between ferumoxytol (FMX) tumor uptake and tumor response to MM-398

  Ferumoxytol uptakes will be associated with change in tumor lesion size. Corrected FMX results (ug/mL) from target lesion(s) at 24-hour scan is used to measure FMX tumor uptake. For the repeated scans performed at the same timepoint, the FMX tumor uptake will be averaged first before summarizing. For patient with multiple target lesions, average corrected FMX results should be used for analysis. FMX uptake will be classified as 'low tumor uptake' or 'high tumor uptake' using overall median as cutoff. Change in tumor size is used to assess tumor response to MM-398. For patient with multiple target lesions, the best change in tumor size achieved should be used. The relationship between dichotomous FMX tumor uptake classification and tumor response to MM-398 will be assessed using Fisher's exact test.

11.3 Secondary Efficacy Analysis

All Phases:

- **To assess tumor response to treatment**

11.3.1 Tumor Response-related Variables

- Investigator determined tumor response assessment

Investigator determined tumor assessments will be performed at baseline and at 8-week intervals following initiation of MM-398. Overall tumor response for post-baseline assessments will be classified as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive

Disease (PD), Not Evaluable (NE) or Non-CR/Non-PD (no-target disease only) per RECIST version 1.1 criteria or modified RECIST criteria for cohort 3 CNS disease only.

For each tumor assessment, investigators will evaluate and report on the CRF a classification of overall tumor response and its components (target lesions, non-target lesions, and new lesions). Main analyses of tumor response related variables will be based on the investigator assessment of tumor response.

Derived efficacy evaluations including progression-free survival, best overall response, and objective response rate will be based on investigator determined tumor response data.

- Radiological tumor response assessment

In addition to investigator determined tumor response assessment, tumor that have FMX uptake measurement will also be measured radiologically in central facility. Response classifications will be algorithmically computed from the data on target lesions, non-target lesions and new lesions. The radiological tumor response will be reported separately for associating with ferumoxytol (FMX) uptake.

11.3.2 Secondary efficacy variables (All Phases)

Secondary efficacy analysis will be based on Investigator determined tumor response assessment following RECIST 1.1. Cohort 3 CNS disease will be analyzed according to RECIST and modified RECIST, separately. The worst case between RECIST and modified RECIST may be reported.

11.3.2.1 Progression-Free Survival (PFS)

PFS is defined as the time in months from first dose of MM-398 to the date of radiologic disease progression by RECIST or mRECIST (cohort 3 CNS disease) per Investigator assessment or death due to any cause, whichever occurs first.

Date of Progression: the earliest date that an overall tumor response of PD or death is recorded. Data handling conventions for determining the date of progression are outlined in Table 3.

If progression is associated with a new lesion, the date of progression is the date when the new lesion was detected, where progression is associated with the sum of target lesions and different lesions are measured on different dates in a given visit, use the earliest date for visit as the date of progression.

For patients who do not have qualifying progressive disease or death, the date of censoring for PFS is the date when the last valid tumor assessment determined a lack of progression. If the last valid tumor assessment involves measurements over multiple days in a visit, the date of the last measurement will be the censoring date. A tumor assessment is considered valid if data has been recorded for all target lesions and absence of new lesions is documented. Date of last non-PD/non-NE assessment is the date of first dose date for patients without a valid post-baseline tumor assessment.

Table 3 Data handling rules for PFS analysis

Condition	Date of Progression or Censoring	Event
No baseline tumor assessments	Date of first dose of MM-398	Censored
Progression documented within 12 weeks* of baseline or the last non-PD/non-NE tumor assessment	Earliest of: • date of radiographic assessment showing new lesion (if progression based on new lesion) or • date of radiographic assessment of target/non-target lesions in which progression is documented	Progression
Death within 12 weeks* of last non-PD tumor assessment without documented progression	Date of death	Progression
Death or first documented progression after 12 weeks* from last non-PD tumor assessment	Date of last non-PD assessment	Censored
None of the following: • documented progression • death • treatment termination • New anticancer therapy started • cancer-related surgery	Date of last non-PD assessment	Censored
Treatment termination for clinical deterioration without documented progression or death	Date of last non-PD assessment or date of first dose of study drug MM-398 if no evaluable post-dose tumor assessment	Censored
Treatment termination for adverse event or other reason without documented progression or death	Date of last non-PD assessment or date of first dose of study drug MM-398 if no evaluable post-dose tumor assessment	Censored
New anticancer therapy started prior to treatment termination without documented progression	Date of last non-PD assessment prior to start of new anticancer therapy or date of first dose of study drug MM-398 if no evaluable post-dose tumor assessment	Censored
Cancer-related surgery prior to documented progression	Date of last non-PD assessment prior to cancer related surgery or date of first dose of study drug MM-398 if no evaluable post-dose tumor assessment	Censored

*16 weeks will be used for PFS sensitivity analysis

As a sensitivity analysis, PFS will also be analyzed following the same censoring rule in table 3 with 16 weeks of baseline or the last non-PD/non-NE tumor assessment time window being applied.

Progression-Free Survival (PFS) will be presented for each cohort and overall for expansion phase.

PFS assessed by investigator will be analysed using Kaplan-Meier method and descriptively summarized at 3 months interval for each dose level cohort. Median PFS time and corresponding 95% confidence limits will be presented.

11.3.2.2 Best Overall Response (BOR)

BOR is defined as the best response per RECIST recorded from first dose of MM-398 until progression or start of new anti-cancer therapy and/or surgery. Designation of SD requires at least one assessment of stable disease at least 4 weeks after starting treatment. Patients with insufficient data for response classification will be classified as Not Evaluable for best overall response in the efficacy evaluable population.

The primary analysis for BOR will be based on the investigator-assessed response. BOR will be summarized by each cohort and overall for expansion phase. The analyses will be performed for efficacy evaluable population.

11.3.2.3 Objective Response Rate (ORR)

ORR is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients, expressed as a percentage. Evaluable patients are the treated patients with measurable disease at baseline. Patients with insufficient data for response classification will be classified as non-responder for objective response in the efficacy evaluable population.

The primary analysis for ORR will be based on the investigator-assessed response. ORR will be summarized by each cohort and overall for expansion phase and exact 95% confidence intervals based on the binomial distribution will be reported. The analyses will be performed for efficacy evaluable population.

11.3.2.4 Clinical Benefit Response (CBR)

CBR_{24} is defined as the proportion of patients with a BOR characterized as a Complete Response (CR) at any time, Partial Response (PR) at any time, or Stable Disease (SD) $\geq$ 24 weeks relative to the total number of evaluable patients, expressed as a percentage. Evaluable patients are the treated patients with measurable disease at baseline.

The primary analysis for CBR will be based on the investigator-assessed response. CBR will be summarized by each cohort and overall for expansion phase and exact 95% confidence intervals based on the binomial distribution will be reported. The analyses will be performed for efficacy evaluable population.

11.3.2.5 Duration of Objective Response (DOR)

DOR is defined as the time from first documentation of response (CR or PR whichever occurs first, by investigator assessment) to the date of disease progression or to death due to any cause, whichever occurs first. Duration of response will be computed only for patients who have CR or PR as best overall response. If progression or death does not occur for a patient with response, the patient's duration of response will be censored in accordance with the rules used for PFS analysis. Duration of objective response will be calculated for all patients that experience documented objective response during the study in weeks as follows:

Duration of DOR (Months) = ((Date of Progression/Death/Censoring Date of First Recorded CR or PR)+1) *12/365.25

The primary analysis for DOR will be based on the investigator-assessed response. DOR will be summarized by each cohort and overall for expansion phase. The analyses will be performed for efficacy evaluable population.

Imaging - Related:

Pilot Phase:

- **To estimate the correlations between FMX-MRI, TAM levels, and tumor levels of irinotecan and SN-38 with administration of MM-398**
  Scatter plot of FMX-MRI vs. tumor SN-38 level, TAM level and irinotecan level will be presented. For FMX-MRI, corrected FMX results across all scanned lesions at the same timepoint for a patient will be used. If there is more than one image data at the same timepoint for a patient, image data will be averaged first before summarizing.

- **To determine the value of FMX-MRI in directing tissue biopsy**
  The value of FMX-MRI in directing tissue biopsy will be evaluated by summarizing the feasibility of ferumoxytol (FMX) quantitation in tumor lesions, feasibility of FMX-MRI to identify tumor associated macrophages (TAM), and the relationship assessment between ferumoxytol (FMX) tumor uptake and tumor response.

Expansion Phase

- **To assess the association between deposition, as visualized by ferumoxytol imaging, and measures of efficacy**
  The association will be performed on per lesion basis. The analysis will be combined into primary endpoint analysis "The Relationship Between Ferumoxytol (FMX) tumor uptake and tumor response to MM-398" in section 11.1

- **To assess the analytical performance of FMX-MRI measurements and optimize FMX-MRI parameterization**
  The analytical performance of FMX-MRI measurements will be evaluated by summarizing phantom slopes and intercepts from all scans per instrument (site) and per instrument type (1.5 vs 3T). For each instrument or instrument type phantom slopes and

intercepts will be summarized per acquisition method (FSPGR vs MGRE) and per phantom type (body, head). The phantom slope over time will be summarized as rate of change (stability).
Heterogeneity of lesion signal on baseline scan and 24h scan repeats will be summarized (interscan lesion signal CV%; FSPGR and avg MGRE). Heterogeneity of signal between MGRE scan repeats will be summarized (intrascan lesion signal CV%).
Optimization of FMX-MRI parameterization will be evaluated by grouping FMX signals at 4 hour and 24 hours relative to the median value observed in the evaluable lesions and comparing these groups with the best change in lesion size seen by imaging (CT/MRI).
Contrast to noise ratios of FMX lesion signals will be evaluated between responding and non-responding lesions (CR/PR) at all scan times.

12 SAFETY ANALYSES

Safety analyses will be based on safety population.

The analysis of safety assessments in this study will include summaries following categories of safety and tolerability data collected for each patient:

- Adverse Events
  - AEs and SAEs
  - AEs leading to discontinuation of study drug
  - TEAE
  - Deaths
- Clinical Laboratory Investigations
- Vital signs
- ECG Investigations
- Pregnancies (if any reported)
- Physical exam

Safety analyses will be presented for each safety population in accordance with the respective study periods (see Section 7.6.3). Safety analyses will be summarized by each cohort and overall for expansion phase.

12.1 Adverse Events

Adverse events will be coded using the MedDRA dictionary. Levels of classification will include primary system organ class and preferred term. In addition, toxicity grading will be assigned according to NCI CTCAE.

General Rules for summarizing AEs:

(1) An AE will be considered as treatment-emergent (TE) if it begins on or after study drug dosing, starts prior to dosing and increases in grade/severity or seriousness after dosing, or starts prior to dosing but the causality changed to “related” after dosing. In case of missing dates, an AE will be considered as treatment-emergent.

(2) In the event of multiple adverse events being reported by the same patient, the most serious causality (related > not related) will be chosen.

(3) In the event of multiple occurrences of the same adverse events being reported by the same patient, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related) will be chosen.

(4) If a patient experiences the same AE (i.e. same preferred term) more than once, they are only counted once under the count for preferred term.

(5) If a patient experiences more than one AE in a particular system organ class, they will only be included once in the count for the system organ class, but will appear in the count for each appropriate preferred term within the system organ class (unless it is the same preferred term).

(6) AEs related to study drug tables include only those AEs with a relationship to study drug of 'related' or if there is a missing relationship on the AE page of the CRF.

(7) For AE severity the following rules will be applied in determining the counts of AEs:

- An individual patient who experiences two AEs of the same preferred term of the same severity will be included once in the appropriate severity count for the particular AE.
- An individual patient who experiences two AEs of the same preferred term but different severity will be included once in the severity count for the higher severity but not in the count for the lesser severity.
- In the total counts for each severity classification, an individual patient who experiences two AEs of different preferred term of the same severity will be included once in the total for the appropriate severity.
- In the total counts for each severity classification, an individual patient who experiences two AEs of different preferred term of different severities will be included once in the total for each of the appropriate severities.

Tabular summaries will be presented for each cohort and overall for expansion phase. Summaries will include the number and percentage of patients and classified by primary system organ class and preferred term. The following summaries will be reported for AEs, TEAE regardless of drug relationship, TEAE related to study drug, TEAE grade 3 and above regardless of drug relationship, TEAE grade 3 and above related to study drug, serious AEs (SAEs), AE leading to study drug discontinuation, and AE leading to death:

- Overall summary of adverse events will descriptively summarize all adverse events, treatment-emergent adverse events (TEAE), serious adverse events (SAEs), TEAE related to study drug, TEAE with CTCAE grade 3 and above, TEAE related to study drug with CTCAE grade 3 and above, TEAE leading to death, TEAE related to study drug leading to death, TEAE related to study drug leading to discontinuation, and TEAE related to study drug leading to dose adjustment (interruption or decrease).
- Summary of TEAE by system organ class (SOC) and preferred term (PT) by decreasing frequency.
- Summary of TEAE by CTCAE grade, SOC and PT, by decreasing frequency.

- Summary of TEAE related to study drug by SOC and PT, by decreasing frequency.
- Summary of TEAE by CTCAE grade 3 and above, SOC and PT, by decreasing frequency.
- Summary of TEAE related to study drug by CTCAE grade 3 and above, SOC and PT, by decreasing frequency.
- Summary of TEAE related to study drug leading to dose adjustment (interruption or decreased), discontinuation and death by SOC and PT, by decreasing frequency.
- Summary of TEAE related to study drug leading to discontinuation and death by SOC and PT, by decreasing frequency.
- Summary of SAE by SOC and PT, by decreasing frequency.
- Summary of SAE related to study drug by SOC and PT, by decreasing frequency.

Listings of all AEs/TEAEs/SAEs will be presented by treatment group and sorted by patient id, start time, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study, onset day relative to the first treatment date of AEs, date of Resolution, AEs, SAEs, related to study drug.

Listing of AE leading to study drug discontinuation and death will be presented in each study period and treatment group.

12.2 Clinical Laboratory Evaluations

Scheduled clinical safety laboratory parameters will be summarized. Absolute laboratory values will be summarized by visit. Maximum and minimum change from baseline laboratory data will be summarized. Baseline will be the last measurement taken prior to the first study drug administration of MM-398. Frequency and percent of abnormal laboratory values will be assessed. Shift to most severe toxicity grade will be summarized. These include:

- **Hematology:** hemoglobin, hematocrit, leukocytes, differential white blood cell count, absolute neutrophil count, platelets.
- **Chemistry:** sodium, potassium, chloride, bicarbonate, alkaline phosphatase, ALT (SGPT), AST (SGOT), uric acid, blood area nitrogen, creatinine, LDH, glucose (random), calcium, magnesium, phosphate, total bilirubin, direct bilirubin, total protein, albumin.
- **Urinalysis:** A urinalysis will include descriptions of color and clarity; pH; specific gravity; and analyses of blood, glucose, ketones and total protein. A microscopic examination of the urine, to include WBC, RBC, bacteria and casts will be performed if the urinalysis is abnormal.

Abnormal lab values will be classified as low (lower than normal limit), normal (within normal range) and high (> upper normal limit). Laboratory values will also be assessed according to NCI CTCAE Version 4.0 or higher, where possible. Abnormal lab values will be flagged (Low [L],

High, [H], abnormal clinically significant [C],) where applicable in the listing. Any unscheduled laboratory assessments will be flagged [U] in the listing.

In addition, a separate listing will be created for all grade 3 and higher post-baseline laboratory observations and any out-of-range values that are identified by the investigator as being clinically significant.

12.3 Vital Signs

Vital signs data will be listed. In the vital signs listings, all values outside the normal ranges will be flagged to indicate whether they are above the upper limit of reference range (H) or below the lower limit of the reference range (L). Vital signs will be tabulated for the change from baseline by timepoint.

12.4 Electrocardiograms

Listings will be presented for ECG data. All ECG results of clinical significance, and those graded as CTCAE Grade 3 will be identified in the listing.

12.5 ECOG Performance Score

ECOG performance score will be summarized by study phase, study period, and study week.

12.6 Physical Examinations

Results of physical examinations will be listed by patient.

12.7 Pregnancies

Patients are to be discontinued from the study if they become pregnant. Pregnancy data will be shown in a data listing if applicable. No special analysis will be performed on the pregnancy data.

13 OTHER ANALYSES

13.1 Pharmacodynamic Marker Analysis

Post-hoc biomarker analysis may be performed. Details of analyses will be documented in a separate document.

14 Population Summary Conventions

- The population analyzed/displayed will be clearly and consistently identified on TLFs and will be identical in name to that identified in the protocol or SAP.

- Population sizes will be presented for each cohort as totals in the column header as (N=xxxx), where appropriate.
- All population summaries for continuous variables will include: n, mean, SD, minimum, and maximum. Other summaries (e.g. median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.
- Summary statistic n values will denote the number of patients with non-missing values.
- Population summaries for categorical variables will include only categories where at least one patient had a response.
- In general, percentages will be rounded and reported to a single decimal point (xx.x%). Where percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1% and percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%, while 0% will be reported as a blank.
- Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). P-values <0.001 will be reported as <0.001.

15 REFERENCES

Awada, A, Garcia, AA, Chan, S, et al. (2013) Two schedules of etirinotecan pegol (NKTR-102) in patients with previously treated metastatic breast cancer: a randomised phase 2 study. *Lancet Oncol*., 14(12): 1216 25

Eisehauer, EA et al. (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur. J Cancer, 45*, 228 - 247.

Kümler, I, Brünner, N, Stenvang, J, et al. (2013) A systematic review on topoisomerase 1inhibition in the treatment of metastatic breast cancer. *Breast Cancer Res. Treat*m 138(2): 347 58.

ICH. (1995, November). E3: Structure and Content of Clinical Study Reports. Retrieved from http://www.ich.org

ICH. (2005, November). The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002879.pdf

US FDA. (2007, May). Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm0715900

US FDA. (1998, September 16). International Conference on Harmonization; Guidance on on Statistical Principles fo Clinical Trials. Federal Register, 63(179), pp. 49583 - 49598.

16 APPENDIX A

From http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin decreased	6.2 mmol/L - < LLN	4.9 mmol/L - <6.2 mmol/L	<4.9 mmol/L	
Hemoglobin increase	↑ in >0 – 2 g/dL above ULN or > BL if BL>ULN	↑ in >2 – 4 g/dL above ULN or > BL if BL>(ULN+2)	↑ in >4 g/dL above ULN or > BL if BL>(ULN+4)	
Lymphocyte decrease	$0.8x10^9$/L – <LLN	$0.5x10^9$/L – <$0.8x10^9$/L	$0.2x10^9$/L – <$0.5x10^9$/L	<$0.2x10^9$/L
Neutrophils decrease	$1.5x10^9$/L – <LLN	$1.0x10^9$/L – <$1.5x10^9$/L	$0.5x10^9$/L – <$1.0x10^9$/L	<$0.5x10^9$/L
Platelets decrease	$75.0x10^9$/L – <LLN	$50.0x10^9$/L – <$75.0x10^9$/L	$25.0x10^9$/L – <$50.0x10^9$/L	<$25.0x10^9$/L
WBC decrease	$3.0x10^9$/L – <LLN	$2.0x10^9$/L – <$3.0x10^9$/L	$1.0x10^9$/L – <$2.0x10^9$/L	<$1.0x10^9$/L
ALT increase	>1 ULN – 3xULN	>3xULN – 5xULN	>5xULN – 20xULN	>20xULN
Alkaline Phosphatase increase	>1 ULN – 2.5xULN	>2.5xULN – 5xULN	>5xULN – 20xULN	>20xULN
AST increase	>1 ULN – 3xULN	>3xULN – 5xULN	>5xULN – 20xULN	>20xULN
Total Bilirubin increase	>1 ULN – 1.5xULN	>1.5xULN – 3xULN	>3xULN – 10xULN	>10xULN
Creatinine increase	>1xBL – 1.5xBL or >1xULN – 1.5xULN	>1.5xBL – 3xBL or >1.5xULN – 3xULN	>3xBL – 6xBL or >3xULN – 6xULN	>6xBL or >6xULN

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Calcium increase	Corrected calcium*: >ULN – <2.9 mmol/L	> 2.9 mmol/L– 3.1 mmol/L	> 3.1 mmol/L– 3.4 mmol/L	>3.4 mmol/L
Calcium decrease	Corrected calcium*: 2.0 mmol/L – <LLN	1.75 mmol/L – <2.0 mmol/L	1.5 mmol/L – <1.75 mmol/L	<1.5 mmol/L
Albumin decrease	3 g/dL - <LLN	2 g/dL - < 3 g/dL	< 2 g/dL	
Magnesium decrease	0.5 mmol/L - <LLN	0.4 mmol/L - <0.5 mmol/L	0.3 mmol/L - <0.4 mmol/L	<0.3 mmol/L
Magnesium increase	>ULN – 1.23 mmol/L		>1.23 mmol/L – 3.30 mmol/L	>3.30 mmol/L
Potassium decrease	3.0 mmol/L - <LLN		2.5 mmol/L <3.0 mmol/L	<2.5 mmol/L
Potassium increase	>ULN – 5.5 mmol/L	>5.5 mmol/L – 6.0 mmol/L	>6.0 mmol/L – 7.0 mmol/L	>7.0 mmol/L
Glucose decrease	3.0 mmol/L - <LLN	2.2 mmol/L – 3.0 mmol/L	1.7 mmol/L - <2.2 mmol/L	<1.7 mmol/L
Sodium decrease	130 mmol/L - <LLN		120 mmol/L - <130 mmol/L	<120 mmol/L
Sodium increase	>ULN – 150 mmol/L	>150 mmol/L – 155 mmol/L	>155 mmol/L – 160 mmol/L	>160 mmol/L
Phosphate decrease	0.8 mmol/L - <LLN	0.6 mmol/L - <0.8 mmol/L	0.3 mmol/L - <0.6 mmol/L	<0.3 mmol/L
Uric Acid increase	>ULN – 0.59 mmol/L		>0.59 mmol/L	

*Corrected calcium (mmol/L) = Ca(mmol/L) + 0.02[40(g/L) albumin(g/L)]; refer to calcium (mmol/L) lab normal range for LLN and ULN values.