



**Nektar Therapeutics**

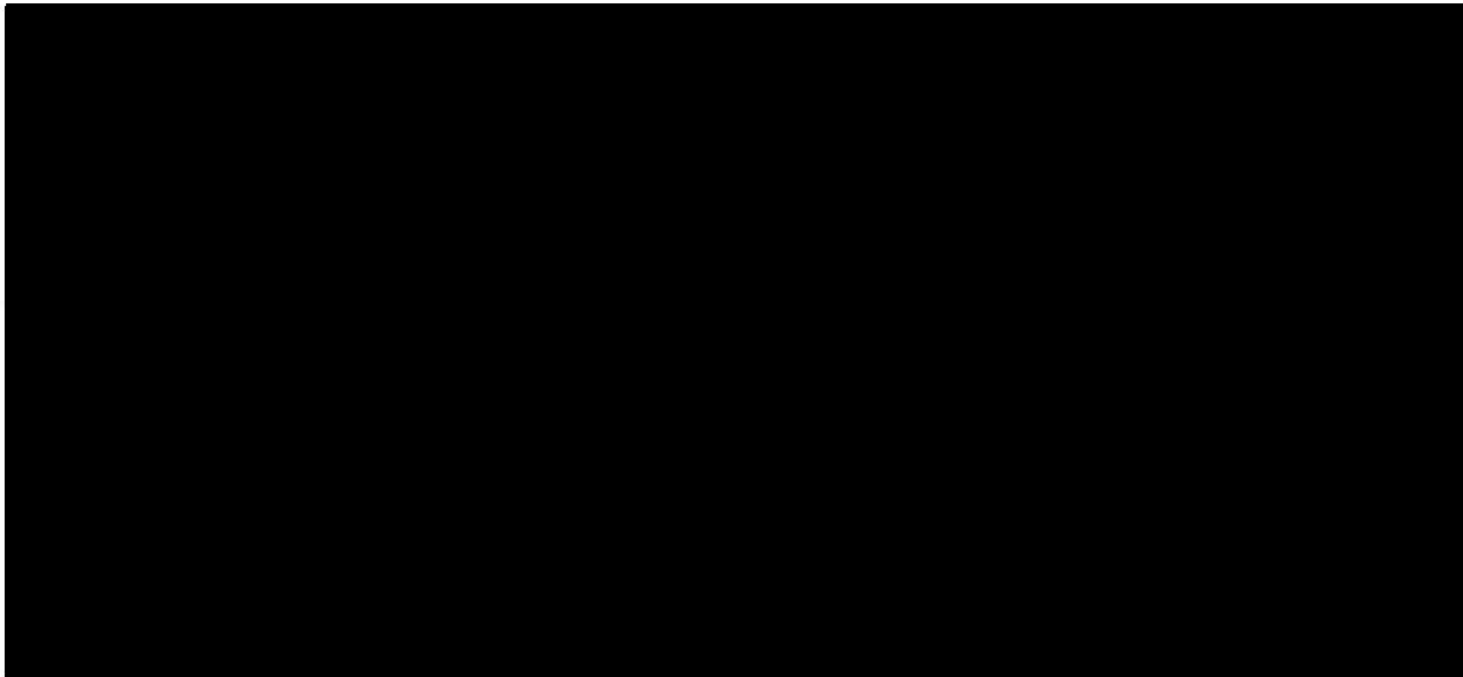
**Statistical Analysis Plan**

**AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY OF NKTR-102 IN  
SUBJECTS PREVIOUSLY ENROLLED IN NKTR-102 STUDIES**

**Protocol Number:** 11-PIR-09, Amendment 2.0, 25 September 2013

**Statistical Analysis Plan Version:** 1.0

**Date:** 10 April 2015



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## 1.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BOR	Best Overall Response
BSA	body surface area
Cmax	maximum concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CPT-11	20-(S)-camptothecin
CRF	Case Report Form
CT	computed tomography
CYP3A4	cytochrome P450 3A4
D5W	dextrose for injection, 5 w/w%
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
Kg	Kilogram
µg	Microgram
m <sup>2</sup>	meters squared

mg	Milligram
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OTC	over-the-counter
PD	Progressive disease
PEG	polyethylene glycol
PK	pharmacokinetic
q14d	once every 14 days
q21d	once every 21 days
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	Serious Adverse Event
SN38	7-ethyl-10-hydroxy-camptothecin
SUSAR	suspected unexpected serious adverse reactions
T <sub>1/2</sub>	terminal elimination phase half-life
ULN	upper limit of normal
UGT1A1	uridine diphosphate-glucuronosyl transferase 1A1
US	United States
USP	United States Pharmacopeia
w×3 q4week	weekly for 3 weeks every 4 weeks
WBC	White Blood Cell

## 2.0 INTRODUCTION

This document describes of the planned statistical analyses of the data captured according to Nektar Therapeutics protocol 11-PIR-09 “An Open-Label, Multicenter, Extension Study of NKTR-102 in Subjects Previously Enrolled in NKTR-102 Studies” amendment version 2.0 dated 25 September 2013.

This study is conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

### **3.0 OBJECTIVES**

#### **3.1 Primary Objective**

The primary objective of this study is to provide access to NKTR-102 to subjects who previously received NKTR-102 in a clinical trial and are without signs of disease progression since receiving NKTR-102.

#### **3.2 Secondary Objectives**

The secondary objectives of this study are: (1) to evaluate the safety of continued exposure to NKTR-102; (2) to observe disease status and survival status in subjects receiving NKTR-102; (3) to evaluate the efficacy of NKTR-102 in subjects with advanced or metastatic solid tumors.

#### **4.0 STUDY ENDPOINTS**

##### **4.1 Endpoint**

- Incidence and duration of toxicities, with severity grading according to NCI-CTCAE v 4.0.
- Tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.



## 5.0 OVERALL STUDY DESIGN AND PLAN

### 5.1 Study Design

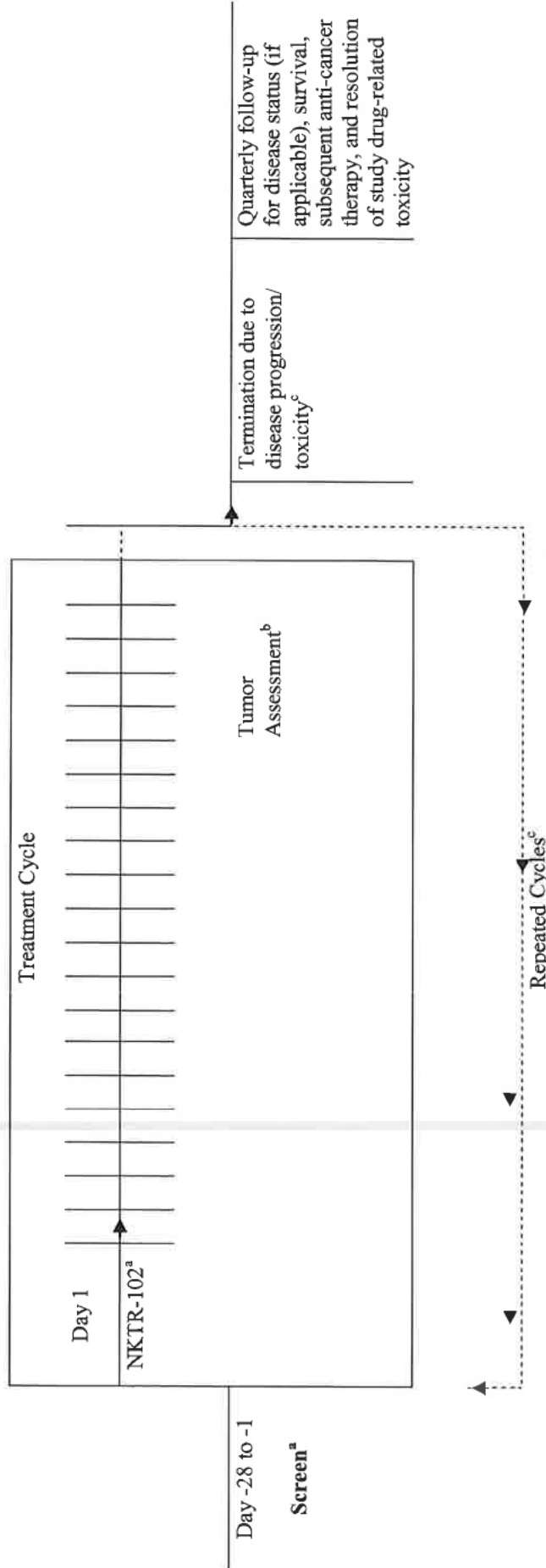
This is a multicenter, open-label, Phase 2 study of NKTR-102 in subjects with solid tumors who received NKTR-102 in a prior Nektar-sponsored clinical study. Following completion of NKTR-102 treatment on a prior NKTR-102 clinical study, subjects will be assessed for eligibility. The Sponsor must approve enrollment of all subjects.

Eligible subjects will continue treatment with NKTR-102 at a dose of 145 mg/m<sup>2</sup> or less in a q21d schedule as outlined in Figure 1: Study Schematic. Subjects who previously received a dose of NKTR-102 at <145 mg/m<sup>2</sup> will continue at the lower dose in this study. Subjects who underwent dose reduction of NKTR-102 due to observed toxicity prior to participation in the Extension study (Protocol 11-PIR-09) will not be re-escalated to the previous dose level upon resolution of the toxicity. Dose escalation for NKTR-102 is not permitted.

NKTR-102 will be administered as an IV infusion over approximately 90 minutes (± 15 minutes) on Day 1 of each 21-day treatment cycle.

Subjects will continue to receive repeated cycles of NKTR-102 treatment until disease progression, unacceptable toxicity, death, withdrawal of consent by the subject, Principal Investigator decision, subject non-compliance, lost to follow-up, or study is terminated by the Sponsor. After discontinuation of NKTR-102, all subjects, except those who withdraw consent from further study follow-up, are to be followed for disease status (as applicable), subsequent anti-cancer therapy, survival status, and resolution of toxicity attributable to study drug (with contact by phone, through a clinic visit, or through review of medical records at least every 3 months) until death.

Figure 1: Study Schematic



a Pre-treatment safety assessments and NKTR-102 administration will occur on Day 1 of each cycle.

b Tumor assessments will be performed as required by standard of care.

c Treatment cycles will be repeated until disease progression, unacceptable toxicity, death, withdrawal of consent by the subject, Principal Investigator decision, lost to follow-up, or study is terminated by Sponsor (See Section 5.1).

## 5.2 Study Medication and Treatment Assignment

Body surface area (BSA) will be determined before the start of each cycle, based on baseline height and current weight. NKTR-102 will be administered as an IV infusion over 90 minutes ( $\pm$  15 minutes). The recommended dose and schedule of NKTR-102 is 145 mg/m<sup>2</sup> q21d, with BSA capped at 2.4 m<sup>2</sup>. Body surface area is to be calculated based on institutional guidelines. Subjects who were previously receiving the 145 mg/m<sup>2</sup> dose will continue to receive it in this extension study in a q21d schedule.

Subjects originally enrolled in a clinical study in which a lower-than-recommended dose was administered (e.g., Protocol 12-102-13 in subjects with impaired liver function) or was being administered after a dose reduction will continue to receive that dose in a q21d schedule in this study if  $\geq$  70 mg/m<sup>2</sup>. For Protocol 12-102-13, the subjects with mild and moderate hepatic dysfunction, as defined in that study, will continue in this study (Protocol 11-PIR-09) to receive originally assigned doses of either 120 mg/m<sup>2</sup> (mild hepatic dysfunction) or 95 mg/m<sup>2</sup> (moderate hepatic dysfunction) in a q21d schedule.

Subjects originally enrolled in a clinical study in which a higher-than-recommended dose was being administered (e.g., Protocol 12-102-12 to explore the effects of NKTR-102 on cardiac function) will receive the recommended dose of NKTR-102 of 145 mg/m<sup>2</sup> in a q21d schedule in this study (Protocol 11-PIR-09).

Subjects who underwent dose reduction of NKTR-102 due to observed toxicity prior to participation in the Extension study [Protocol 11-PIR-09] will not be re-escalated to the previous dose level upon resolution of the toxicity. Dose escalation for NKTR-102 is not permitted.

## 6.0 STATISTICAL CONSIDERATIONS

### 6.1 General Considerations

Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum and maximum). The mean and median will be presented to one decimal place beyond which the data were captured. The standard deviation will be presented to two decimal places beyond which the data were captured. The minimum and maximum will be presented to the precision with which the data were captured.

Categorical variables will be presented as frequency counts and percentages. A row or column denoted 'Missing' will be included in count tabulations where necessary to account for dropouts and missing values. Percentages will be rounded to 1 decimal place and the percent will be suppressed when the count is zero. The denominator will be the number of patients in that dose schedule within the population of interest unless otherwise noted.

All analyses will be summarized for all patients (Total) and by dose level if sample size allows. Data listings will be created to support each table and to present all data. Data listings will be presented by subject number (combination of original NKTR-102 study ID, subject and site ID).

Neither hypothesis testing nor a specific sample size is required for this study.

We will use the term "Original NKTR-102" when referencing the study where a subject first exposed to NKTR102 before rolling over to current study, "Current" to indicate 11-PIR-09 (extension) study and "Overall" to indicate information inclusive of the original NKTR-102 and current throughout this document. The default implication is "Current", when no study specific information is specified,.

### 6.2 Analysis Populations - Current

**Enrolled Population:** All patients who have provided an informed consent are included.

**Safety Population:** The Safety Population consists of all patients who receive at least one dose (or partial dose) of study drug (NKTR-102) under this study.

### 6.3 Analytic Definitions

**General:**

- Age: integer of (Date informed consent signed (Current)– Date of birth) / 365.25.

- Study Day 1: Day 1 is the date of Cycle 1 Day 1 dosing date within Current study.
- Baseline (Current): Baseline will be defined as the last non-missing assessment on or before the study drug administration (Day 1).
- Study day of Current: For post-treatment events, study day is calculated as (visit/assessment date – date of current study first dose of cycle 1 study drug administration) + 1. For pre-treatment events, study day is calculated as visit date – date of Day 1. There is no study day zero.
- Study Day since First Dose of Original NKTR-102: study day is calculated as (visit/assessment date of current study – date of 1<sup>st</sup> dose of the original NKTR-102 study) + 1.
- Study Day since Last dose of Original NKTR-102: study day is calculated as (visit/assessment date of current study – date of last dose of the original NKTR-102 study) + 1.
- 

## Exposure

### Current:

- Exposure Duration (days): Date of last dose – date of first dose (Cycle 1 Day 1) of current study + 21.
- Number of cycles: Total number of complete or partial treatment cycles the patient received.
- Cumulative dose (mg): Total actual dose (mg) the patient received across all cycles, defined as the sum of actual dose (mg) received across all cycles.
- Duration of infusion: Completion time of infusion – start time of infusion.
- Calculated cumulative dose level ( $\text{mg}/\text{m}^2$ ): Cumulative dose (mg) divided by the average BSA ( $\text{m}^2$ ) across all cycles.
- Dose intensity ( $\text{mg}/\text{m}^2/\text{week}$ ): [Calculated cumulative dose level ( $\text{mg}/\text{m}^2$ ) / exposure duration (days)] x 7.
- Expected dose intensity ( $\text{mg}/\text{m}^2/\text{week}$ ): initial planned dose ( $\text{mg}/\text{m}^2$ ) / 3; planned dose will be 145, 120 or 95  $\text{mg}/\text{m}^2$ .
- Relative dose intensity (%): Dose intensity ( $\text{mg}/\text{m}^2/\text{week}$ ) / Expected Dose intensity ( $\text{mg}/\text{m}^2/\text{week}$  at enrollment) x 100.

Overall (Original plus Current):

The exposure duration, number of cycles, cumulative dose, calculated cumulative dose level from 1<sup>st</sup> dose exposure of the original NKTR-102 study to last exposure of current study will also be calculated.

#### 6.4 Handling of Missing Data

- If AE is marked as continuing from prior study as recorded in the CRF and Start day of AE is missing, no imputation will be done, otherwise:
  - Missing day of month will be imputed as the first of the month. Missing month will be imputed as July if the year is before Day 1.
  - If the reported month of occurrence of AE is after the month of Cycle 1 Day 1 dose then day will be imputed as the first day of the month of occurrence of AE.
  - If the reported month of occurrence of AE is the month of Cycle 1 Day 1 dose then the missing day will be imputed as the same day as Cycle 1 Day 1.
- For duration of AEs, partially or completely missing dates for stop of AE, will be imputed as follows:
  - Missing day, month, and year are not allowed and should be queried. In case of non-resolution of missing month and/or year, no imputation will be performed.
  - If the day and/or month is missing, but year is present, the last day of that month and December, the date of discontinuation from the study, or the date of death, whichever is earlier, will be used as the stop date.

No imputation of other missing data is planned.

## 7.0 STATISTICAL ANALYSIS

### 7.1 Patient Disposition

A summary of patient disposition will display the number of patients by original NKTR-102 study entered and by dose level received in this study. The number of enrolled, discontinued from the treatment and exited the study and reasons for discontinuation will be tabulated. Disposition data will be presented in a data listing.

### 7.2 Protocol Deviations

Patients with important protocol deviations will be listed. Protocol deviations by severity and type will be included in the listing.

### 7.3 Demographics and Disease Characteristics

The following data will be summarized and listed for safety population:

Demographics (Current): age (years), sex, race, ethnicity.

Disease characteristics from Original NKTR-102: tumor type, stage, time since initial diagnosis and time since metastatic diagnosis to original NKTR-102 study will be imported from original NKTR-102 study. The values are imputed as below.

Time since initial diagnosis (years) in Original NKTR-102:  $(\text{Date informed consent signed in Original NKTR -102 Study} - \text{Date of initial diagnosis}) / 365.25$ , rounded to one decimal place.

Time since initial metastasis diagnosis (years) in Original NKTR-102 Study:  $(\text{Date of informed consent date in Original NKTR - 102 Study} - \text{Date of diagnosis of metastatic disease}) / 365.25$ , rounded to one decimal place.

#### 7.3.1 Medical History

No medical history data was collected in current study except AE continuing from Original NKTR-102 study at study entry will be collected in AE CRF. No medical information listing will be provided.

AEs that are ongoing at the time of study entry will be summarized by SOC, preferred term and severity grade.

## **7.4 Treatments and Medications**

### **7.4.1 Prior and Concomitant Medications**

No prior and concomitant medications are collected for this study. Any use of prohibited concomitant medications will be recorded in the protocol deviation log.

## **7.5 Exposure**

Exposure to study drug in current study will be listed and summarized in terms of exposure duration, number of cycles, cumulative dose (mg), average dose per infusion ( $\text{mg}/\text{m}^2$ ), dose intensity ( $\text{mg}/\text{m}^2/\text{week}$ ), and relative dose intensity will be calculated for treatment cycles received in this study. The number of patients with dose reduction, dose interruption, and dose delay will be tabulated along with their reason. Overall duration, cycles and cumulative dose will also be computed for all treatment received since initiation of the NKTR-102 of the Original study.

## **7.6 Efficacy Analysis**

Tumor response will be assessed by the investigator according to the frequency that patient's standard of care allows. Baseline will be the assessment at screening visit. Data on the best response and disease progression (per physician assessment) will be collected according to RECIST criteria version 1.1 (Eisenhauser et al., 2009). Tumor assessment and responses at the baseline and subsequent visit will be presented in a listing. Best overall response (BOR) by investigator assessment will be summarized. Time to progression and survival time will be calculated from first dose of original NKTR-102 study enrollment. Time to progression is defined as time from date of first dose of original NKTR-012 study to the 1<sup>st</sup> date of progressive disease (PD) per investigator assessment in current study. Patients without PD will be censored in last visit/follow-up date. Time to death is defined as time from date of first dose of original NKTR-102 study to death date. Patients without death date will be censored in last visit/follow-up date.



## 8.0 SAFETY ANALYSIS

The safety data will include AEs and serious adverse events (SAEs). Summaries will use the Safety Population and will be presented overall. All safety data will be presented in data listings.

### 8.1 Adverse Events

Adverse events will be coded by SOC and preferred term using MedDRA, version v 16.0. Adverse event severity will be based on NCI CTCAE Grade (version 4.03).

A treatment-emergent AE (TEAE) is commonly defined as an AE that was not present prior to treatment with study drug, but appeared following treatment or was present at treatment initiation, but worsened during treatment. In current study, all AEs marked as continuing “No” and having an AE start date on and after informed consent date of extension and at least one dose of study treatment in extension study will be counted as TEAE. An AE that was marked as continuing from original Nektar sponsored study will not be a TEAE in the Extension Study as it has been counted as TEAE in the original NKTR-102 study.

If the start date of an AE is incomplete and cannot be categorized as occurring before or after the first dose, the AE will be considered as TEAE. Start time of AE will not be used to classify TEAE.

Adverse event data will be descriptively evaluated by treatment arm(dose level) and for overall patients. Incidence of TEAEs by MedDRA SOC, preferred term, and relationship (Related) to study drug will be summarized. Adverse event incidence rates will be summarized with frequency and percentage. For patient level of summaries, patients with multiple occurrences of events of the same preferred terms and SOC will be counted once at the highest Grade and the closest relationship to study drug for each preferred term and system organ class. Adverse events that are reported as possibly, probably, or definitely related to study drug will be counted as related to study drug. AEs with a missing relationship will be considered “Related” for this summary.

The following adverse events summaries will be provided:

- TEAEs by System Organ Class and Preferred Term
- TEAEs by System Organ Class and Preferred Term and CTCAE Grade
- Serious TEAEs by System Organ Class and Preferred Term
- Serious TEAEs by System Organ Class and Preferred Term and CTCAE Grade

- TEAEs Related to Study Drug by Preferred Term and by Descending Incidence of Overall Patients
- TEAEs by Preferred Term and by Descending Incidence of Overall Patients
- Serious TEAEs by Preferred Term and by Descending Incidence of Overall Patients
- Serious TEAEs by Preferred Term by Tumor Type by Descending Incidence of Overall Patients
- Serious TEAEs Related to Study Drug by Preferred Term and by Descending Incidence of Overall Patients
- Grade 3 or Higher TEAEs by Preferred Term and by Descending Incidence of Overall Patients
- TEAEs Leading To Study Drug Discontinuation by System Organ Class and Preferred Term and CTCAE Grade
- TEAEs with Fatal Outcome by System Organ Class and Preferred Term.

In addition, TEAE of interest may be grouped and summarized using higher MedDra hierarchies or sponsor defined groupings

The following data listings will be produced:

- All AEs
- SAEs
- TEAEs Leading to Study Drug Reduction, Delay Interruption or Discontinuation
- TEAEs With Fatal Outcome
- TEAE Leading to Death
- Deaths

## 9.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

## 10.0 REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

**ATTACHMENT 1: TABLE AND LISTING SHELLS**

Table and listings shells will be stored in a separate file.

