Cover Page

Phase I Study of Intraperitoneal Cantrixil in Patients with Persistent or Recurrent Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer

NCT02903771

Statistical Analysis Plan: V1.2: 05 March 2020

STATISTICAL ANALYSIS PLAN

NVGN-002-101

PHASE I STUDY OF INTRA-PERITONEAL CANTRIXIL IN PATIENTS WITH

PERSISTENT OR RECURRENT OVARIAN CANCER, FALLOPIAN TUBE CANCER OR

PRIMARY PERITONEAL CANCER.

AUTHOR: JISHO JOSE

VERSION NUMBER AND DATE: V1.2, 05MAR2020

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.2 (Dated 05MAR2020) for Protocol NVGN-002-101 Version 4, 30 APR 2018

	Name	Signature	Date
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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:			
Position:			
Company:			
Approved By:			
Position:	Clinical and Regulatory Affairs Director		
Company:	Novogen		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
V1.0	21JUL2017	Vishali Vijayanagaram	Not Applicable – First Version
V1.1	24JAN2020	Jisho Jose	Latest IQVIA SAP template used
V1.2	**05MAR2020**	Jisho Jose	Added the analysis for part A + part B combined

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, and safety data for Protocol NVGN-002-101. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol Version 4.0, dated Apr 30, 2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

- To determine the maximum tolerated dose (MTD) of Cantrixil when delivered as a single agent, administered intraperitoneally, at a weekly administration frequency.
- To evaluate the safety and tolerability of Cantrixil delivered via intraperitoneal administration as a single agent and in combination with standard chemotherapy, when administered weekly.
- To characterise the pharmacokinetics (PK) of intraperitoneal Cantrixil when delivered as a single agent and in combination with standard chemotherapy.

2.2. SECONDARY OBJECTIVES

- To evaluate the progression free survival (PFS).
- To evaluate the time to paracentesis and the volume of malignant ascites drained at each paracentesis event (for those patients with malignant ascites).
- To evaluate the potential anti-cancer activity of Cantrixil using Response Evaluation Criteria in Solid Tumours (RECIST) criteria, version 1.1 and CA-125 measurements.
- To evaluate the change in cancer antigen 125 (CA-125) in peripheral blood before and after treatment with Cantrixil.

2.3. EXPLORATORY OBJECTIVES

- To evaluate the safety, tolerability, PK, and activity of Cantrixil when administered intraperitoneally as a single agent and in combination at a twice weekly administration frequency
- To evaluate the change in the number of circulating epithelial tumour cells (CETCs) in peripheral blood and malignant ascites (if present) before and after treatment with Cantrixil.
- To evaluate the clonogenicity of CETCs in peripheral blood and malignant ascites (if present) before

and after treatment with Cantrixil.

- To evaluate the expression of stem cell markers, CD44 and ALDH, in colonies isolated in the clonogenicity assays.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This study is a progressive design with 2 discrete Parts (Part A: Dose escalation, Part B: Dose expansion). The overall study schema is presented in Figure 1 of the protocol.

3.2. SCHEDULE OF EVENTS

Table 4 Schedule of Assessments

	Screening[#]	Part A and B: Cycle 1			Part A and B: Cycles 2 to 8			Continued Access	[4]Off Therapy/ End of Therapy
		Week 1	Week 2	Week 3	Week 1	Week 2	Week 3	Weeks 1,2,3	
Cantrixil Administration		Day 1 (+/- 1 day)	Day 8 (+/- 1 day)	Day 15 (+/- 1 day)	Day 1 (+/- 1 day)	Day 8 (+/- 1 day)	Day 15 (+/- 1 day)	Days 1,8,15 (+/- 1 day)	
Informed consent	X								
Catheter/port placement	X[a]								
Demographics	X								
Medical history, including number, type of prior therapies, start and stop dates	X								
Prior and concomitant medication	X[a]	X[a]	X	X	X	X	X		X
Physical examination	X[a]	X[a]	X	X	X	X	X	As per Standard of Care	X
Vital signs	X[a]	X[a]	X	X	X	X	X		X
Height	X								
Weight	X[a]	X[a]			X				
Pregnancy testing	X	X			X				X
ECOG Performance Status	X[a]	X[a]	X	X	X	X	X		X
Safety Laboratory assessments[f]	X[a]	X[a]	X	X	X	X	X		X
CA-125 Testing	X	X	X	X	X	X	X		X
Urine – dip stick	X[a]	X[a]	X	X	X	X	X		X
Triplicate 12-Lead electrocardiogram	X	X			X				
AE evaluation		X	X	X	X	X	X	X	X
Radiologic evaluation	X[b]						X[b]	As per SOC	X[b]
Tumour measurements	X[b]						X[b]		X[b]
Pharmacokinetic studies		X[c]			X[c]	X[c]			
Biomarker Samples	X[e]				X[f]				X[f]

AE: Adverse event; CT: Computed Tomography; ECOG: Eastern Cooperative Cancer Group; MRI: Magnetic Resonance Imaging; PI: Principal Investigator;
[#]The screening period is up to 28 days before the Cycle 1 Day 1 dose of Cantrixil.

a These assessments may coincide, for example if patient already has a port then the pre-study/eligibility assessments may occur on the same day as the first day of Cantrixil administration. Otherwise, it is anticipated that there will be a delay between the pre-study/eligibility assessments and the first day of therapy to allow for the placement of the port/catheter.
b Radiologic evaluations and subsequent tumour measurements should be conducted at the end of each six-week period, coinciding with the end of each two cycles of therapy. The subsequent cycle of therapy should not proceed until this assessment has been evaluated because clear tumour progression may preclude further treatment on this study. The PI can use the imaging modality of preference (either MRI or CT) but the same modality must be used for all time-points.
c Pharmacokinetic samples are collected in these weeks per the schedule described in Table 5.
d The "End of Therapy/Off Therapy" assessments may coincide with the assessments performed at one of the other designated time-points.
e Biomarker samples are collected at screening, end of Cycle 2 (most conveniently collected on Day 1of Cycle 3 before IP administration) and End of Therapy.
f Safety assessments as per Section 8.4 and table below. All assessments should be completed on Days 1, 8 and 15 for Parts A and B.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The MTD population will include all patients who experienced DLTs in Cycle 1/Part A, **as determined by the clinical team**. The safety, tolerability and MTD data sets regarding the Cycle 1/Part A will be used to determine MTD from this analysis population.

4. ITT POPULATION DEFINITION IN PROTOCOL IS REPLACED WITH FULL ANALYSIS POPULATION IN SAP.PLANNED ANALYSES

The final analyses will be performed for this study.

4.1. DATA SAFETY MONITORING COMMITTEE/BOARD (DSMC/B)

This study will utilise a Data Safety Monitoring Committee/Board (DSMC/B) throughout the study. The membership and governance of this committee are outlined in a separate charter. The study SAP will not cover the DSMC/B analysis requirement.

4.2. INTERIM ANALYSIS

There is no interim analysis planned for this study

4.3. FINAL ANALYSIS

The final analyses will be performed for this study after completion of the study and when all collected data is validated, the database will be locked, pursuant to the prior approval by the Sponsor. All details regarding the statistical analysis other than PK and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan (SAP) prepared by IQVIA and approved by the Sponsor before database lock.

5. ANALYSIS SETS

5.1. MAXIMUM TOLERATED DOSE (MTD) POPULATION

The MTD population will include all patients who experienced DLTs in Cycle 1/Part A as determined by clinical team. The safety, tolerability and MTD data sets regarding the Cycle 1/Part A will be used to determine MTD from this analysis population.

5.2. SAFETY (SAF) POPULATION

The SAF population will include all enrolled patients who receive at least 1 dose of study treatment. All safety analyses will be conducted on this population.

5.3. PHARMACOKINETIC (PK) POPULATION

The PK population will include all SAF patients who have had at least 1 PK assessment. All PK analyses will be conducted on this population.

5.4. FULL ANALYSIS POPULATION

The Full Analysis Population (FAS) population will include all enrolled patients who receive at least 1 dose of study treatment and from whom at least 1 post-baseline efficacy measurement is obtained. All efficacy analyses will be conducted on this population and will be based on the actual dose level/single-weekly or twice weekly doses of Cantrixil at which each patient has been treated.

6. GENERAL CONSIDERATIONS

Derivation of the Pharmacokinetic (PK) parameters and the PK summary figures as well as the statistical analysis of the PK variables, will be the responsibility of the clinical pharmacokineticist at TetraQ (The University of Queensland, Brisbane, Queensland, Australia). The efficacy and safety summaries and data listings will be the responsibility of the study biostatistician at IQVIA.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct. The changes will be documented in the IQVIA “Changes to Planned Statistical Analyses Form”.

6.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including number of contributing observations (n), mean, standard deviation (SD), CV, median, minimum, and maximum values.

6.2. TREATMENT SUMMARIZATION

In general, data will be summarised by following groups:

1. by dose cohort of Part A patients,

2. All patients in Part B and those in Part A who were treated at the MTD and overall subjects (part A+part B subjects combined)

These two set of subjects are grouped under two columns for analysis.

6.3. PRECISION

Safety and efficacy variables including derivations thereof, will be reported to the same precision as the source data.

For the reporting of descriptive statistics, the mean will be presented to one digit more precision than the source data, whereas standard deviation and standard error will be presented to two digits more precision than the source data. The minimum, median, maximum and confidence intervals will be presented to the same precision as the source data.

6.4. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

6.5. BASELINE

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the first intake of study medication (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the value of interest and the corresponding baseline value.

6.6. UNSCHEDULED VISITS DATA

Unscheduled measurements will not be included in summary statistics.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

Post-Baseline Value at Visit X – Baseline Value

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. MISSING DATA

No missing data will be imputed.

8. DISPOSITION AND WITHDRAWALS

All patients who received study medication will be accounted for in this study. Patient disposition will be tabulated with the number of patients who are enrolled, dosed, completed the treatment, completed the study, the reason for discontinuation of study and treatment and different population set. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each patient.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAF population.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years)
- Race
- Ethnicity
- Screening Weight (kg)
- Screening Height (cm)
- Screening BMI (kg/m^2)
- Childbearing Potential
- ECOG Performance Status
- Tumour Stage at Diagnosis
- Tumour Stage at Study Entry
- Tumour type
- Histological Sub-Type
- Grade
- Breast Cancer Susceptibility Gene (BRCA) Status
- Duration of Disease

9.1. DERIVATIONS

- BMI (kg/ m2) = weight (kg)/ height (m)2
- Height (m) = height (cm) x 0.010

- Height (m) = height (in) x 0.0254
- Weight (kg) = weight (lb) x 0.45359237

10. PROTOCOL DEVIATIONS

Treatment delays of up to three weeks are allowed without being classified as a protocol deviation for Part A, Cycle 1. Protocol deviations are not captured in CRF and not analysed. Only a listing from CTMS will be provided.

10.1. DEVIATIONS RELATED TO STUDY CONDUCT

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedure requirements. The noncompliance may be either on the part of the patient, the site PI, the study site staff or related to study procedures. Any patient enrolled who does not meet eligibility criteria will be considered an enrollment deviation.

11. DISEASE, SURGICAL PROCEDURE AND MEDICAL HISTORY

Disease history, anti-cancer surgical procedure history, radiotherapy history and previous cancer treatment regimens will only be listed as collected in the eCRF for SAF population.

Patient Medical History information will be presented for the SAF population.

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary version 20.0

- Medical History conditions are defined as past and/or concomitant diseases and reported at Screening.
- Presented by System Organ Class (SOC) and Preferred Term.

12. MEDICATIONS

Prior, concomitant and standard chemotherapy medications will be presented for the SAF and coded using World Health Organisation (WHO) Drug Dictionary (DD) version WHODDMar2017. The medications will be summarised using the WHO Preferred Term. Listings for all reported medications will be provided for the SAF population.

- 'Prior' medications are medications which stopped prior to the first dose of Cantrixil. Previous cancer treatment regimens along with no of lines will be summarized. Previous platinum therapy (which has the word 'platin') will be summarized and the time to disease progression after platinum therapy will also be analysed.

- 'Concomitant' medications are medications which on-going at the time of the first dose or is started after

the first dose of Cantrixil.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in weeks will be presented for the SAF.

The date of first study medication administration will be taken from the eCRF form. The date of last study medication will be taken from the eCRF form.

Number of Cycles, Total number of cycles, Administered dose by cycle, Total dose administered by cycle, dose adjustment with reason and duration of exposure will be summarised descriptively.

Total Dose administered (mg) = sum over all weeks of actual dose received (mg).

13.1. DERIVATIONS

Duration of exposure (weeks) = (date of last study medication administration – date of first study medication administration + 1)/7

14. PRIMARY OUTCOMES

14.1. PRIMARY OBJECTIVES

The primary analysis will be performed on MTD population.

For determination of the MTD, individual patient data from the dose escalation part (Cycle 1/Part A) will be reported. In addition, for the final statistical analysis, the following will be analysed:

- At each dose level, the number and proportion of patients in the MTD population who experience a DLT during the DLT evaluation period (Cycle 1/Part A). Since the number of subjects experiencing DLT is less, a listing will be provided.
- At each dose level, the number and proportion of treatment emergent AEs (TEAEs) experienced by patients in the MTD population during the DLT evaluation period (Cycle 1/Part A). All the events from the first dosing till Cycle 2 Day 1 is considered for DLT evaluation. If Cycle 2 is not given then events till 7 days after the last doing in Cycle 1 is considered.

The MTD will be determined according to the dose-escalation plan (Refer protocol table 3). The MTD is defined as the highest dose level at which no more than 1 patient out of 6 patients treated in a cohort and evaluable for DLT determination experiences a DLT during Part A/ Cycle 1.

15. PHARMACOKINETIC ANALYSIS

The PK assessment results will be described in a PK study report prepared by TetraQ at completion of the study

16. SECONDARY OUTCOMES

16.1. SECONDARY OBJECTIVES

The secondary analyses will be performed on ITT population.

16.1.1. SECONDARY OBJECTIVES VARIABLES & DERIVATIONS

16.1.1.1. Progression Free Survival

The progression free survival (PFS) will be summarised as mentioned in section 6.2. Details of the calculation of progression free survival and censoring rules are presented below.

PFS (in months) is defined as the time from first dose to the date of first disease progression as defined by RECIST version 1.1 and/or Gynecological Cancer Intergroup (GCIG) criteria or death from any cause (whichever occurs first). If a patient has neither disease progression nor died, PFS will be censored on the date of the last disease assessment (from end of study form or visit form whichever is the maximum). PFS (in months) is calculated as follows:

PFS = (date of event/censoring - date of first dose + 1) / 30.4375

		Date of event /censoring	Censoring
Disease progression /Death		Date of disease assessment/ Death Date	No
No assessment available but progression was specified as reason for study/treatment discontinuation		Date of discontinuation	No
No progressive disease	No disease response assessment after the first dose and no progression specified at study discontinuation	Date of discontinuation	Yes
	No disease response assessment after the first dose and patient is alive at study discontinuation	Date of discontinuation	Yes
	Otherwise	Date of last disease assessment	Yes

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve. If the no of censored is more than 50% of the subjects, then the medial estimate will not be considered as realiable.

16.1.1.2. Time to paracentesis

The time to paracentesis will be measured as the time from the first recorded paracentesis event until the next paracentesis event for malignant ascites drainage. The time between all subsequent paracentesis events in the sequence for each patient with malignant ascites will also be recorded. The first recorded paracentesis event may be immediately before the first dose of Cantrixil but this may not be true for all patients.

The overall number of paracentesis events will be summarised and changes in frequency during the period of treatment for each patient described.

The graph to be plotted will depict any changes in the frequency of paracentesis events by illustrating the normalised change in time between events vs event (n). The time between the first recorded paracentesis event and the next one will be set at “1” then all subsequent tim te between events will be normalised to this “baseline”.

16.1.1.3. Volume of Malignant Ascites

The volume of abdominal fluid will be measured by estimating the volume of malignant ascites drained at each paracentesis event and the normalized volume to “baseline” will be summarised as mentioned in section 6.1. “Baseline” will be the volume recorded at the first paracentesis event captured, this may be immediately before the first dose of Cantrixil but not necessarily. This “baseline” volume will be set at “1” and all subsequent volumes normalised to this “baseline”.

The graph to be plotted will depict the normalised volume at each event vs event (n) for each patient with malignant ascites.

16.1.1.4. Disease Response

Disease response will be measured using RECIST version 1.1 criteria; during Follow-up, response may be also assessed using the GCIG response criteria that incorporates CA-125 measurements.

The disease response within the time from start of treatment till end of the study will be considered. The disease response for target lesions, non-target lesions, CA-125 response and overall response will be summarised as mentioned in section 6.1 using frequency and percentage of patients in each response category.

Best overall response will be derived using the protocol Table 8 algorithm for determining the best overall response in patients without initial measurable disease and who are evaluable per the definition above. Patients that have measurable disease at study entry can be evaluated during Follow-up using both RECIST 1.1 and CA-125 criteria as summarised in protocol Table 9. In patients who have measurable disease by both criteria, the date of response will be the date of the earlier of the 2 events. Overall Response assessment using RECIST and GCIG at scheduled visits and Best overall response at the end of trial using RECIST and GCIG will be summarised descriptively and listed.

16.1.1.5. CA-125 level

Concentration of CA-125 in peripheral blood will be assayed in local laboratories using locally validated assays at baseline and then weekly during treatment, at the End of Therapy and during Follow-up. CA-125 level will be summarised using descriptive statistics as mentioned in section 6.1.

17. EXPLORATORY OBJECTIVES

17.1. EXPLORATORY OBJECTIVES VARIABLES & DERIVATIONS

The first exploratory objectives to evaluate safety, tolerability, PK, and activity of Cantrixil when administered intraperitoneally as a single agent and in combination at a twice weekly administration frequency will be summarised same as explained in primary, secondary and safety objectives analysis methods. Other objectives will be summarised as follows:

17.1.1. CIRCULATING EPITHELIAL TUMOUR CELLS

Enumeration of CETC in peripheral blood and malignant ascites (if present) will be assayed using the MAINTRAC® CETC Count method by Genostics or similar methodology. This method uses a fluorochrome-labelled antibody against surface epithelial antigen (EpCam) to tag CETCs. Image analysis allows CETC numbers to be calculated in relation to blood volume over the course of treatment. Samples will be assayed at baseline, at the end of Cycle 2 and at the End of Therapy.

Number of circulating epithelial tumour cells (CETCs) in peripheral blood and malignant ascites (if present) before and after treatment with Cantrixil will be summarised descriptively and listed for the FAS population.

17.1.2. CLONOGENICITY OF CETCS

Clonogenicity of CETCs in peripheral blood and malignant ascites (if present) will be measured using the MAINTRAC® Tumour Sphere Units assay by Genostics or similar methodology. Samples will be assayed at baseline, at the end of Cycle 2 and at the End of Therapy. Clonogenicity of CETCs will be summarised descriptively and listed for the ITT population.

17.1.3. EXPRESSION OF STEM CELL MARKERS, CD44 AND ALDH

Expression of stem cell markers in the isolated colonies will be measured using labelled antibodies and scanning fluorescent microscopy techniques by Genostics or similar facility. A descriptive summary and listing of patients with stem cell markers ALDH1 and CD44 (%) and number of colonies and number of colonies positive per mL of blood and/or per CETC for a stem cell marker will be summarised descriptively.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the safety population.

There will be no statistical comparisons for safety data.

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0

18.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity during or after the first dose of Cantrixil.

An overall summary of number of patients within each of the categories described in the sub-section below will be provided as specified in the templates.

Listings will include TEAEs and non-TEAEs, including event start/stop date/time, onset day, severity, seriousness, relationship to investigational product, action taken and outcome.

18.1.1.1. Dose Limiting Toxicities

A listing of patients presenting DLTs occurring during Cycle 1/Part A will be summarised by SOC and PT for the groups mentioned in the section 6.2. The MTD determining set will be used.

18.1.1.2. Severity

Severity of AEs will be graded using the National Cancer Institute (NCI)-CTCAE version 4.03 severity grading scale.

If a patient reports a TEAE more than once within that SOC/ PT, the TEAE with the worst case severity will be used in the corresponding severity summaries.

18.1.1.3. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as ‘Yes’ or ‘No’ to the question: ‘Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?’. **T**EAEs with a missing relationship to study medication will be regarded relationship as ‘Yes’. If a patient reports a TEAE more than once within that SOC/ PT, the TEAE with the worst-case relationship will be used in the corresponding relationship summaries.

18.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to Study Discontinuation are those events which are recorded on the AE eCRF where the End of Study eCRF Primary Reason for Premature Discontinuation is 'Adverse Event,' and the AE Number matches the AE eCRF. A listing of AEs leading to study discontinuation will be prepared.

18.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the Adverse Event eCRF. A summary of serious TEAEs by SOC and Preferred Term will be presented by dose cohort and twice weekly dose cohort.

18.1.4. Adverse Events Leading to Death

AEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be presented by dose.

18.2. Laboratory Evaluations

Results from the safety laboratory will be included in the reporting of this study for the assessments given in the protocol section 8.4

Presentations will use SI Units.

The following summaries will be provided for laboratory data:

- Actual and change from baseline (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to abnormal criteria (for quantitative measurements and categorical measurements)
- Listing of patients with the actual measurements by each lab category/parameters
- Listing of patients meeting markedly abnormal criteria for each lab category/parameter

18.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the lab vendors and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

Clinical laboratory reference/normal ranges will be listed. Lab data with '<' or '>' symbols along with the results cannot be interpreted and hence cannot be included in the analysis.

18.3. ECG EVALUATIONS

Results from Electrocardiogram (ECG) will be included in the reporting of this study.

All time point recordings will be obtained in triplicate. Only average of these records will be displayed in the listing and used in tables.

The following ECG parameters will be reported for this study:

- Ventricular Rate (bpm)
- PR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)
- RR Interval (msec)
- QTcF (msec)
- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (ANCS)
  - Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data for the groups mentioned in section 6.1.:

- Actual and change from baseline for each cycle (for quantitative measurements)
- Listing of patient ECG data.

18.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (resp/min)
- Body Temperature (ºC)
- Weight (kg)

The following summaries will be provided for vital signs data by dose cohort and twice weekly dose cohort.

- Actual and change from baseline for each cycle
- Listing of patient vital signs data

18.5. PHYSICAL EXAMINATION

The following Physical Examination measurements per investigator's judgment will be reported for this study as collected on the Physical Examination (PE) eCRF unless otherwise specified below:

- General Appearance
- Head
- Ears
- Eyes
- Nose
- Throat
- Respiratory system (chest)
- Cardiovascular system
- Gastrointestinal/ Liver

- Musculoskeletal/Extremities
- Dermatological/Skin
- Thyroid/Neck
- Lymph Nodes
- Neurological/Psychiatric
- Other

The following summaries will be provided for physical examination data for the groups mentioned in section 6.2.

Incidence of Normal, Abnormal, Not Done at all the collected weeks.

A listing with all data collection at various visits along with abnormality details will also be presented.

18.6. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Eastern Cooperative Oncology Group (ECOG) performance status (Grade 0 - Grade 5) will be for the groups mentioned in section 6.2 by presenting the number and percentage of patients in each category for the safety population.

18.7. OTHER ANALYSES

A listing of patients who had a closed catheter or port inserted will be presented for the data collected from the port insertion eCRF page.

A list of patients with the pregnancy report will be presented for the data collected in the eCRF.

Tumour measurements for target lesions sum of diameters will be summarised using descriptive statistics for actual and change from baseline at the scheduled assessments for the groups mentioned in section 6.2.

Tumour measurements for non-target lesions will only be listed by patient.

19. REFERENCES

NA

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following Global Bios > Processes > GBIOS Processes - Implementation Guidelines and Templates > General Guidelines and Templates > Output Conventions.

DATES & TIMES

Depending on data available, dates will take the form yyyy-mm-dd.

SPELLING FORMAT

English US (or English UK)

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Part A followed by Part A. Under Part A, subjects will be sorted by the ascending order of dose group assigned to.
- center-subject ID,
- date (where applicable),

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.) For cases where start dates are stop dates are missing, they will be presented as '-/-'

ALGORITHM FOR PREVIOUS / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

For time to disease progression after previous platinum therapy calculation, if the date part of treatment end regimen is partial i.e only date unknown, then it will be considered as 15thof that month for the calculation of time to disease proression after platinum therapy.