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

NCT02903771

Study Protocol
Date 30 April 2018

Phase I Study of Intra-peritoneal Cantrixil in Patients with Persistent or Recurrent Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer.

Protocol Number: **NVGN-002-101**
IND Number: **123275**

Product: **Cantrixil (TRX-E-002-1 in 20% Dexolve-7)**

Indication: **Ovarian, Fallopian Tube, or Peritoneal Cancer**

Clinical Phase: **Phase I**

Principal Investigators:

Principal Investigator
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A/Prof Jim Coward (Lead PI in Australia)

Sponsor: **Kazia Therapeutics Limited**
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Australia

Version: **4.0**

Date: **30 April 2018**

DOCUMENT HISTORY

Version	Date	Reason for amendment	Summary of changes	Substantial amendment (Y/N)
2.0	07 September 2016	Incorporate changes as per FDA recommendations	Define allowed combination chemotherapies and dosing schedules. Update eligibility criteria as per FDA advice. Include assessment by the DSMC/B of Cantrixil monotherapy PK data before beginning combination therapy for each patient. Amend errors or ambiguities in language for improved clarity.	Y

3.0	26 June 2017	Add a mechanism to allow extended access beyond the first 8 cycles; Remove Part C; Incorporate Changes as per HREC recommendations	Add an additional extended access cohort to the study. Remove all references to Part C. Update names and contact details of Principal Investigators and Sites. Update language to improve clarity of protocol and correct errors that had been identified.	Y
4.0	30 April 2018	Update Novogen name change approved at AGM held on 15th November 2017; Update Corporate Address post move 5th February 2018; Remove Biomarker sample from part B Update Quintiles name change announced November 2017	Change all references of Novogen to Kazia Therapeutics to reflect the approved name. Update the Corporate address to Three International Towers Level 24, 300 Barangaroo Avenue Sydney NSW 2000, Australia; Remove all references to the collection of the Biomarker sample in Part B. Changed all references of Quintiles to IQVIA	Y

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2 TABULATED PROTOCOL SUMMARY

Name of Sponsor/Company:	Kazia Therapeutics Limited
Name of Finished Product(s):	Cantrixil
Name of Active Ingredient(s):	TRX-E-002-1 (in 20% Dexolve-7)

Title of Study:

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

Principal Investigators:

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Investigational Site:

The study will be conducted in approximately 5 to 6 study centres in Australia and the United States (US).

Clinical Phase:	Phase I

Objectives:

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.

Secondary Objectives

- To evaluate 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.

Exploratory Objectives

- To evaluate the safety, tolerability 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.

Methodology:

This study is a progressive design with 2 discrete Parts (Part A: Dose escalation, Part B: Dose expansion). Cycle 1/Part A is a dose-finding assessment (dose escalation) to establish the MTD of Cantrixil when administered as a single dose once a week for 3 weeks. Cycle 2/Part A continues with 3 additional weekly doses of Cantrixil as a monotherapy before an assessment of disease response. In Cycles 3 to 8/Part A, patients will be administered the same once-weekly dose of Cantrixil they tolerated in Cycles 1 and 2 (tolerance defined as no dose limiting toxicities [DLTs] or unacceptable adverse events [AEs]) in combination with standard chemotherapy agent(s), in order to assess the safety and tolerability of Cantrixil in combination therapy. Standard chemotherapy drugs will be administered at the standard efficacious dose and dosing schedule to maintain optimum benefit of known therapeutic agents for patients. Treating physicians may choose the combination therapy from the list in Table 1 taking into consideration factors such as pre-existing comorbidities, prior toxicities and responses as well as patient and physician preferences.

Combination chemotherapy may not be administered until 24 hours after administration of Cantrixil to avoid any adverse drug-drug interactions. All combination therapies and concomitant medications must be diligently recorded in the patients' electronic case report form (eCRF).

Once the MTD has been determined in Part A/Cycle 1, an additional 12 patients will be recruited in an expansion cohort for Part B. These patients will receive 2 cycles of Cantrixil monotherapy at the MTD, followed by up to 6 cycles of combination therapy, selected by the treating physician from Table 1.

Patients enrolled into the respective parts of the study may not receive treatments under different parts of the protocol e.g., if a patient enters Part A, she may not also continue to Part B even if she is considered to have completed Part A.

To accommodate the intraperitoneal administration of Cantrixil, an in-dwelling, closed catheter or port will be inserted if the patient does not already have one. For intraperitoneal ports, the minimum period between port placement and the first administration of Cantrixil must not be shorter than 7 days. For other intraperitoneal access devices, the period may be shorter if adequate stability and/or healing of the delivery system's insertion site is confirmed by the treating physician.

Patients should begin protocol treatment within a maximum of 28 days of enrolment (i.e., signing of consent form).

Patients will start at Dose Level 0 (see Table 2) which is calculated to be the human equivalent of 10% of the STD10 dose in rats (dose is 1/10 the severely toxic dose in 10% of rats tested). Dose levels -1 and -2 will only be activated if there are 2 DLTs at the Dose Level 0 and -1, respectively. Single patient cohorts will be treated with increasing doses of Cantrixil until an AE is observed during Part A/Cycle 1 that meets the definition of a DLT or, in the opinion of the Data Safety Monitoring Committee/Board (DSMC/B) and the Investigator, warrants observing additional patients at this dose level; at this point the study will revert to a 3+3 rules-based dose escalation study. The decision to expand from single patient cohorts to 3 patient cohorts is critical for the safety of participants and will be made with input from the Investigator and DSMC/B responsible for this study. Once the study enters a 3+3 rules-based design, the

study will not revert back to single patient cohorts.

If any unacceptable AE or DLT is observed in any cycle, patients may be dose reduced to the next lower dose level of Cantrixil for subsequent doses of therapy. If a second unacceptable AE or DLT is observed during any cycle within the same patient, treatment for the patient with Cantrixil will be discontinued. Investigators may continue with the standard chemotherapy at their discretion and if it is considered safe and in the patient's best interest.

If any of the following unacceptable AEs or DLTs are observed and unless clearly unrelated to study treatment (e.g., disease progression), treatment at the currently allocated Cantrixil dose will be paused. At this point a dose reduction may be considered or the treatment may be terminated, depending on what is considered by the investigator to be in the participant's best interest.:

- Hematologic toxicity
    - Grade 4 neutropenia, lasting at least 5 days,
    - Grade 3 or Grade 4 neutropenia associated with fever >38.5°C,
    - Grade 4 thrombocytopenia lasting at least 5 days,
    - Grade 3 thrombocytopenia associated with severe bleeding in the opinion of the Investigator,
    - Dose delay of ≥3 weeks due to failure to recover counts.
- Any Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Grade 3 or Grade 4 non-haematological toxicity except:
    - Alopecia
    - Grade 3 abdominal pain deemed related to the port or catheter as determined by the treating physician
    - Grade 3 anorexia
    - Grade 3 fatigue
    - Grade 3 nausea and/or vomiting, or diarrhoea, lasting ≤48 hours with or without maximal medical management.
    - Grade 3 dehydration as a result of nausea and vomiting
    - Grade 3 constipation
    - Grade 3 metabolic abnormalities [hypokalaemia, hypomagnesemia, hypocalcaemia, hypophosphatemia]) that recovers to Grade 1 or less within 48 hours with or without medical management
- Other serious adverse events (SAEs) which, in the opinion of the treating Investigator, necessitate temporary or permanent cessation of administration
- Treatment delays of ≥3 weeks due to any non-haematological toxicity will constitute a DLT

All patients who discontinue (i.e. are now Off Therapy/ End of Therapy) from the study treatment will progress to follow-up unless the patient withdraws consent.

The initiation of each new cycle of Cantrixil will be at the discretion of the Investigator and will depend on the potential or measurable benefit to the patient assuming continued tolerability and adequate organ function.

Cantrixil treatment will be stopped due to RECIST version 1.1 defined disease progression observed after at least 2 cycles of combination therapy, recurrence of unacceptable toxicity after 1 Cantrixil dose reduction or patient consent withdrawal. Note that patients with progressive disease at the end of

2 cycles of Cantrixil monotherapy will not be taken off therapy if Cantrixil has been well tolerated. Pre-clinical data would suggest that the maximum benefit from Cantrixil will be realised as a combination therapy, hence all patients will have the opportunity to continue receiving Cantrixil as a combination therapy. Additionally, patients receiving combination therapy that are observed to have progressive disease as identified by RECIST version 1.1 criteria but who, in the opinion of the Investigator, continued to derive clinical benefit may continue Cantrixil treatment. Patients may also be discontinued from study treatment if the Investigator considers continuing therapy is not in the patient's best interest. All patients discontinued from study treatment (i.e. are now Off Therapy/ End of Therapy) will progress to follow-up unless the patient withdraws consent.

Tumour assessment via radiological imaging will be conducted during screening and every 6 weeks after the start of therapy, i.e. at the end of monotherapy and then after every 2 cycles of combination therapy. The screening period is up to 28 days before the Cycle 1 Day 1 dose of Cantrixil. Either contrast-enhanced magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) may be used, but once a modality is used at baseline this must be used consistently for that patient throughout their participation on the study. Other imaging is not mandatory, but may be performed if clinically indicated.

Adverse events will be monitored for the duration of the study from the time of informed consent. Blood samples will be collected weekly for standard safety testing, or more frequently if clinically relevant, during the study. Additional volumes of blood will be collected before and after administration of Cantrixil for PK analysis (4 mL per time point as per the proposed PK schedule [Table 5]) and for any exploratory studies (at baseline, end of Cycle 2 and End of Therapy, 15 to 20 mL at each time-point).

Part A (Dose escalation of Cantrixil as a monotherapy):

Cycle 1

Following placement of a port or catheter, eligible patients will be administered a single dose of the study treatment Cantrixil (TRX-E-002-1 formulated in Dexolve-7) intraperitoneally once a week for 3 weeks. Patients will be monitored for DLTs over the 21-day cycle (Cycle 1).

Blood samples will be collected weekly at each scheduled visit for standard safety testing, or more frequently if clinically relevant. Results of the safety assessments must be available prior to Cantrixil administration to ensure that all assessments still meet inclusion criteria as described in Section 6.2.1 and it is safe to proceed to the next dose of treatment. Treatment delays of up to three weeks are allowed for recovery without being classified as a protocol deviation or a dose limiting toxicity.

Patients will continue to be monitored until they meet the study discontinuation criteria but will only be evaluable for DLTs that define the MTD of Cantrixil as a monotherapy during Cycle 1/Part A.

Patients will start at Dose Level 0 (see Table 2) which is calculated to be the human equivalent of 10% of the STD10 dose in rats (dose is 1/10 the severely toxic dose in 10% of rats tested). Dose levels -1 and -2 will only be activated if there are 2 DLTs at the Dose Level 0 and -1, respectively. Single patient cohorts will be treated with increasing doses of Cantrixil until an AE is observed during Part A/Cycle 1 that meets the definition of a DLT or in the opinion of the DSMC/B and the Investigator, warrants observing additional patients at this dose level; at this point the study will revert to a 3+3 rules-based dose escalation study (see Section 6.1.2). The decision to expand from single patient cohorts to 3 patient cohorts is critical for the safety of participants and will be made with input from the Investigator and DSMC/B responsible for this study (see Section 6.1.1).

Cycle 2

Patients that are still on study treatment at the end of Cycle 1/Part A will receive another cycle of Cantrixil monotherapy with once weekly dosing before disease assessment. Note that a disease

assessment will be conducted at the end of monotherapy but patients will not automatically be removed from therapy at this time-point if they have progressive disease as defined by RECIST version 1.1 criteria. This is because the preclinical data strongly suggests that the benefit of Cantrixil will most likely be realised as a combination therapy. All patients will, therefore, have the opportunity to progress to a combination therapy with Cantrixil.

Patients that have not discontinued from the study at the end of Cycle 2 will proceed to Cycles 3 to 8/Part A of the study.

Cycles 3 to 8 (Cantrixil in Combination with Standard Chemotherapy)
Patients that progress to Cycles 3 to 8/Part A will continue on the same dose level of Cantrixil that they tolerated in Cycles 1 and 2/Part A, but in combination with systemic chemotherapy selected from Table 1 by the treating physician/Investigator.

During Cycles 3 to 8/Part A, patients will be administered Cantrixil once per week for each 21-day cycle. In addition to Cantrixil, patients will receive the chemotherapy selected by the Investigator according to the schedule in Table 1. Before administration of the combination chemotherapy, the PK results for each patient from Part A/ Cycle 1 will be reviewed by the DSMC to ensure that the PK profile of Cantrixil is indeed compatible with the proposed schedule for the combination chemotherapy agent.

With the anticipated PK profile of Cantrixil, combination therapy should not be administered until 24 hours after any dose of Cantrixil to avoid any adverse drug-drug interactions. All combination therapies and concomitant medications must be diligently recorded in the patient's eCRF.

Part B (Expansion Cohort at MTD):
Once the MTD has been established, an expansion cohort will be recruited at the MTD. An additional 12 patients will be recruited in this cohort on top of those recruited in Part A at the MTD. These patients will be subjected to the same intervention described above with 2 cycles of monotherapy followed by up to 6 cycles of combination therapy.

Continued Access for Patients:
Patients who complete the planned 8 cycles of treatment and in whom the Investigator feels there has been clinical benefit, have the option to continue to receive Cantrixil. This will be based on discussion between the Sponsor and the Investigator, all of which must be documented.

It is at the discretion of the Investigator whether this continued treatment is a maintenance monotherapy or a combination chemotherapy.

All patients that are provided continued access to Cantrixil are considered to be ongoing participants in this trial and hence, must agree to on-going data collection for monitoring safety, progression and survival.

Number of Subjects:

Six to 54 (includes up to 42 in Part A and12 in Part B) patients with persistent or recurrent ovarian cancer, fallopian tube cancer or primary peritoneal cancer.

Main Criteria for Inclusion:

Patients with the following disease criteria are eligible for this study:

1. Patients must have recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer. The original diagnosis must be verified by a histology report. All histological sub-types and all grades of disease are eligible to participate; grade, histological sub-type and breast cancer susceptibility gene (BRCA) status must be recorded at study entry.
2. Patients must be female and at least 18 years old. Patients may be women of child-bearing potential as long as they are not pregnant or breast-feeding and able to adopt adequate

contraception as described in section 6.2.3.1.

3. Patients with malignant ascites are eligible to participate; paracentesis will be conducted before the administration of Cantrixil. Drainage of the maximum volume of ascites should be performed according to local standard operating procedures before administration of Cantrixil.
4. Patients must have completed at least two (2) or more prior regimens (including adjuvant therapy) for their ovarian, Fallopian tube or primary peritoneal cancer prior to participation in the current study; all prior therapies must be recorded at baseline. Patients that have received prior intraperitoneal therapy are eligible for this study. Patients should have failed standard of care drugs prior to being eligible to be part of the proposed study.
5. Patients must have platinum-resistant relapsed disease, platinum refractory disease, or have documented intolerance to platinum therapy. Patients will not be eligible based on rising CA-125 levels alone, patients must have other clinical symptoms (such as malignant ascites) or radiological tumour measurements that support disease recurrence or progression.
6. At least 4 weeks must have passed from any previous therapy and any toxicities from prior therapies (6 weeks for bevacizumab, nitrosoureas or mitomycin C treatment) must have resolved to less than or equal to Common Terminology Criteria for Adverse Events (CTCAE version 4.03) Grade 1 with the exception of alopecia, Grade 2 prior platinum-therapy related neuropathy and Grade 2 anaemia.
7. Patients must have a performance status of Eastern Cooperative Oncology Group (ECOG) 0 to 2 and, in the Investigator's opinion, be able to complete at least a major part of the study.
8. Patients must be willing and able to undergo insertion of a port or catheter for intraperitoneal access; the type of port or catheter used will be recorded.
9. Patients may have measurable or non-measurable disease; disease response and progression will be measured and assessed according to RECIST version 1.1 criteria using contrast CT, MRI and CA-125 measurements.
10. Patients must have acceptable hepatic and marrow function as defined below:
11. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
12. Platelets $\geq 100 \times 10^9$/L
13. Total bilirubin; <2.5 times the institutional upper limit of normal (ULN)
14. Haemoglobin (Hb) of >10 g/dL; patients with Hb >9g/dL will be considered for this study if they have not received a transfusion or other bone marrow support. Patients with Hb >10 g/dL that have received a recent transfusion will only be eligible if there has been a wash-out period of 7 days for rhesus factor and 10 days for platelet transfusions, respectively.
15. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT])/ alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase [SGPT]) ≤2.5 x institutional ULN.
16. Serum creatinine <1.5 x ULN
17. Prothrombin time (PT) or international normalised ratio (INR) ≤1.5 x ULN and activated partial thromboplastin time (aPTT) ≤1.5 x ULN if not on anticoagulation treatments.
18. Patients must be willing and able to comply with all study requirements, including treatment timing and/or nature of required assessments and treatment at designated study centre.
19. Each participant must be adequately informed about the purpose of the study; potential benefits

and risks; their right to refuse participation or to withdraw consent at any time; institutional affiliation and potential competing interests of the researcher; and sources of study funding and have signed and dated a written informed consent form.
Main Criteria for Exclusion: 1. Patients who have had chemotherapy, biologic therapy, immunotherapy, or radiotherapy within 4 weeks (6 weeks for bevacizumab, nitrosoureas or mitomycin C) prior to entering the study. 2. Patients must not have had major surgery within 4 weeks prior to screening. 3. Patients may not have received any other investigational medicinal products (IMPs) or participated in any other interventional clinical research studies within 4 weeks of the first Cantrixil administration. 4. Patients receiving any medications or substances that are strong inhibitors or inducers of cytochrome P450 (CYP)1A2, CYP2B6 and CYP3A4 or those substances with narrow therapeutic index are not to be enrolled. These compounds are prohibited from screening until completion of end of therapy or first post-treatment follow-up visit. For a list of prohibited medications see the University of Indiana Clinical Pharmacology Department's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/). Note: the use of paclitaxel is allowed, but only 24 hours after Cantrixil administration. 5. Patients deemed by the Investigator to be at high risk of bowel perforation or obstruction are excluded, including but not limited to any one or more of the following; • Patients with a recent history (previous 12 months) of bowel obstruction prior to study entry • Patients with CT scans that suggest invasion of bowel by tumour • Patients with symptoms to suggest impending bowel obstruction • Patients with prior whole abdominal radiotherapy • Patients with chronic inflammatory bowel diseases such as Crohn's disease or ulcerative colitis 6. Patients may not have uncontrolled or severe systemic diseases or psychiatric conditions, which in the treating physician's opinion makes it unsafe for the patient to participate in the study or would hinder compliance with the protocol. Screening for chronic conditions is not required. 7. Patients that are pregnant, lactating, or unable to adopt adequate contraception are excluded. Women of childbearing potential must have a negative pregnancy test within 7 days prior to screening. 8. Patients with active hepatitis B or C. 9. Patients known to have tested positive for human immunodeficiency virus (HIV) 10. Patients with a known hypersensitivity to or serious reaction to benzopyrans are excluded.
Test Product, Dose and Route of Administration: Cantrixil, escalating doses from 0.24 mg/kg to 20 mg/kg, intraperitoneal administration
Duration of Treatment: The target number of cycles is eight; 21 days per cycle, followed by a maximum of 3 months' follow-up. On-going treatment with Cantrixil, beyond the planned 8 cycles of treatment scheduled in Parts A and B

of this study, is an option for patients who, based on the local Investigator's opinion, are benefiting from treatment. All requests for continued access require discussion with the Sponsor.

Endpoints

Primary:

1. Determination of the MTD of Cantrixil using standard safety monitoring assessments when administered as a monotherapy.
2. Description of the PK of Cantrixil when administered as a monotherapy and in combination with standard chemotherapy agent(s).

Secondary:

1. PFS will be measured as the time from treatment start until objective disease progression as defined by RECIST version 1.1 and/or GCIG criteria.
2. The time to paracentesis will be measured as the time from treatment initiation until the next paracentesis event for ascites.
3. The volume of abdominal fluid will be measured by estimating the volume of malignant ascites drained at each paracentesis event.
4. Disease response will be measured using RECIST version 1.1 criteria; during Follow-up, response may be also assessed using the Gynecological Cancer Intergroup (GCIG) response criteria that incorporates CA-125 measurements (see Appendix C).
5. 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.

Exploratory:

1. Determination of the optimum dose and administration schedule (i.e. weekly vs twice weekly administration) using standard safety monitoring assessments, PK measurements and tolerability of delivery in the study centre.
2. 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.
3. 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.
4. Expression of stem cell markers in the isolated colonies will be measured using fluorescein isothiocyanate-labelled (FITC-labelled) or alternatively labelled antibodies and scanning fluorescent microscopy techniques.

Criteria for Evaluation

Pharmacokinetics:

Pharmacokinetic samples will be collected at the time points indicated in the proposed PK schedule for each subject:

At each of the sampling periods a blood sample will be collected into a 4mL dipotassium ethyllenediaminetetraacetic acid (EDTA) tube and the sample processed to plasma. The plasma samples will be divided into a primary and back up sample and stored frozen at -80°C. The primary sample will subsequently be shipped to the contracted bioanalytical laboratory. The samples will subsequently be analysed for TRX-E-002-1 using a liquid chromatography tandem mass spectrometry (LC-MS/MS) based method which has been previously validated for determination of TRX-E-002-1 concentration in

human plasma.

Efficacy:

Although disease response is not the primary endpoint of this study, patients with measurable disease will be assessed for disease response by standard RECIST version 1.1 criteria. For the purposes of this study, patients should have their disease burden evaluated at baseline and re-evaluated every 6 weeks. Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumours (RECIST) committee, version 1.1; the Gynecological Cancer Intergroup (GCIG) response criteria that incorporates CA-125 measurements may also be used during Follow-up. As per RECIST version 1.1, the patient's entire tumour burden will be documented at baseline and followed throughout the study as well as CA-125 levels. Only those patients that have received at least 1 cycle of chemotherapy, and have had at least 1 post-treatment disease evaluation, will be considered evaluable for disease response.

Safety:

Physical examination, vital signs, laboratory tests, including urinary analysis, 12-lead electrocardiograms (ECGs), and AE monitoring.

Statistical Methods

Determination of sample size:

For this Phase I dose-escalation study to determine the MTD of Cantrixil as a monotherapy and to investigate the safety and tolerability when combined with standard chemotherapy, an appropriate sample size is not statistically determined.

The dose-escalation Part A/Cycle 1 of the study is designed to determine the MTD of Cantrixil as a monotherapy in patients with ovarian cancer. The planned dose levels include 0.24, 0.6, 1.25, 2.5, 5, 10 and 20 mg/kg. From the initial dose level, single patient cohorts will be used until an AE is observed during Part A/ Cycle 1 that meets the definition of a DLT or warrants further examination in the opinion of the Principal Investigator and the DSMC/B and then the dose escalation will follow the 3+3 dose escalation model to treat up to 3 to 6 patients at each escalating dose level. After Cycle 2, patients will continue at the same dose level combined with standard chemotherapy through Cycles 3 to 8 in Part A of the study. Patients who haven't experienced a DLT but who do not complete Cycle 1 of therapy will be replaced. To establish the MTD in Part A of the study, up to 42 patients will be enrolled. An expanded cohort with 12 patients will be enrolled and treated at the MTD in Part B of the study.

The total sample size may be up to 54 patients (up to 42 in Part A and 12 in Part B) enrolled into this study.

Analysis populations:

Maximum Tolerated Dose (MTD) population: The MTD population will include all patients who experienced DLTs in Cycle 1/Part A, and those who received all three weekly doses of study treatment in Cycle 1/Part A. The safety, tolerability and MTD data sets regarding the Cycle 1/Part A will be used to determine MTD from this analysis population.

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

Pharmacokinetic (PK) population: The PK population will include all SAF patients who have had at least one PK assessment. All PK analyses will be conducted on this population.

Intent-to-Treat (ITT) population: The ITT population will include all enrolled patients who receive at least one dose of study treatment and from whom at least one 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.

Statistical Analysis:

As appropriate, variables will be summarised descriptively (frequency and percent will be summarised for categorical variables; mean, standard deviation [SD], median, minimum, and maximum will be presented for continuous variables) by study visit and by treatment group, including dose group and monotherapy vs combination therapy. All study data will be listed by subject.

MTD

For determination of the MTD, individual subject data from the Part A/ Cycle 1 dose escalation part will be reported.

In addition, for the final statistical analysis, the following will be analysed:

- At each dose level, the number and proportion of subjects in the DLT population who experience a DLT during the first DLT evaluation period (Cycle 1/Part A).
- At each dose level, the number and proportion of treatment-emergent AEs (TEAEs) experienced by subjects in the DLT population during the first DLT evaluation period (Cycle 1/Part A).

The MTD will be determined according to the dose-escalation plan described above.

The MTD is defined as the highest dose level at which no more than 1 subject out of 6 subjects treated in a cohort and evaluable for DLT determination experiences a DLT during Part A/ Cycle 1.

Safety and tolerability

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarised by System Organ Class (SOC), Preferred Term, and dose cohort. Severity of AEs will be graded using the National Cancer Institute (NCI)-CTCAE version 4.03 severity grading scale. Adverse events will be further summarised by maximum severity and relationship to study medication. Prior and concomitant medications will be summarised by dose cohort. Standard chemotherapy medications will be separately summarised by dose cohort. Safety laboratory tests and vital signs assessments, will be summarised by treatment using statistics for continuous or categorical data, as appropriate.

DLTs, safety and tolerability data will be summarised for Cycles 1 to 2 and Cycles 3 to 8 separately at MTD from Part A and Part B study, as appropriate. A detailed Statistical Analysis Plan (SAP) including dictionaries used for coding and software used will be finalised prior to clinical database lock of the study.

Pharmacokinetic Parameters

Summary statistics will be presented for Cantrixil (TRX-E-002-1) plasma concentrations at each scheduled time point by dose cohort (for example, mean, geometric mean, median, SD, standard error of the mean [SEM], coefficient of variation [CV] and range). Summary statistics will also be presented by dose cohort for all TRX-E-002-1 PK parameters, including

- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$),
- Maximum plasma concentration (C_{max}) and
- Time to maximum plasma concentration (t_{max}), plus if estimable:
- Area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$),

- Apparent terminal half-life ($t_{1/2}$),
- Clearance (CL) and
- Volume of distribution (Vd).

All concentrations below the limit of quantification and/or missing data will be labelled as such in the concentration data listings. Concentrations below the limit of quantification which are after C_{max} will be treated as missing in summary statistics and for the calculation of PK parameters. Pharmacokinetic parameters will be determined by standard non-compartmental pharmacokinetic analyses using Phoenix 64 WinNonLin software.

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

3 LIST OF ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical agent
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical (system)
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{0-last}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
BRCA	Breast cancer susceptibility gene
CA-125	Cancer antigen 125
CD44+ve	Ovarian cancer stem-like cells
CD44-ve	Ovarian somatic cancer cells
CETC	Circulating epithelial tumour cell
CI	Confidence interval
CL	Clearance
CSP	Clinical study protocol
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
C_{max}	Maximum plasma concentration
DBP	Diastolic blood pressure
DLT	Dose limiting toxicity
DSMC/B	Data Safety Monitoring Committee/Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Cancer Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EU GMP	European Union – Good Manufacturing Practice
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good manufacturing practice
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IC_{50}	Median inhibitory concentration

ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Internal Review Board
ITT	Intent to treat
IV	Intravenously
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LDH	Lactate dehydrogenase
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
NCI	National Cancer Institute
NOEL	No Effect Level
PK	Pharmacokinetic
OTC	Over the counter
PFS	Progression Free Survival
PT	Prothrombin time
QC	Quality control
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAF	Safety (population)
SAP	Statistical analysis plan
SD	Standard deviation
SBP	Systolic blood pressure
SEM	Standard error of the means
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
SOC	System organ class
STD10	Severely toxic dose in 10% of rats tested
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Apparent terminal half life
t_{max}	Time to maximum plasma concentration
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
US	United States
Vd	Volume of distribution
WHO-DD	World Health Organization Drug Dictionary

4 INTRODUCTION

4.1 Background Information

Cantrixil is an investigational drug product consisting of the active ingredient, TRX-E-002-1, formulated in the cyclodextrin molecule, Dexolve-7. The active pharmaceutical ingredient, TRX-E-002-1, is the active enantiomer of a super-benzopyran molecule that has been identified as having potent anti-cancer activity against a broad range of cancer phenotypes. It has been selected particularly for its potent cytotoxicity against the two main sub-populations of ovarian cancer cells, namely ovarian cancer stem-like (CD44+ve) cells and ovarian somatic cancer (CD44-ve) cells. Against CD44-ve and CD44+ve cells, observed median inhibitory concentration (IC_{50}) values for TRX-E-002-1 ranged from 23 to 109 nM.

TRX-E-002-1 induces cell death by both caspase-dependent and caspase-independent apoptosis. The molecular target remains unconfirmed, but similar to other drugs of this class and based on *in silico* modelling, it may involve tumour-associated NADH oxidase (ENOX2) and disruptions to trans-membrane electron-transport mediated energy production (Brown et al., 2008). Recent mechanistic studies in ovarian cancer demonstrated that TRX-E-002-1 induces caspase-mediated apoptosis. All pro-apoptotic factors (Bax, bid, XIAP) were up-regulated along with significant up-regulation of pJun, suggesting activation of stress pathways associated with mitochondrial depolarisation. Akt was unaffected.

The super-benzopyran family of drugs, including TRX-E-002-1, is derived from a family of naturally occurring plant diphenolic (benzopyran) compounds, (i.e., genistein and daidzein). Compounds such as genistein are plant hormones with pleiotropic characteristics in plants and can up- and down-regulate a range of enzymes and gene transcription factors. Similarly, benzopyrans have proven to have a wide range of pleiotropic effects in animals including humans and have been the subject of drug development programs across various cancer and degenerative disease indications.

Pharmaceuticals in this class include Phenoxodiol, Triphendiol and two further investigational agents, ME-143 and ME-433. Starting with the first-in-class, Phenoxodiol, and ending with ME-433, these compounds demonstrate increasing potency in *in vitro* studies. Human clinical trials have successfully been completed for all of these agents over the last decade. No significant safety issues were identified with Phenoxodiol in over 800 patients treated with the drug either orally or intravenously (IV) on a continuous basis for periods up to several years (Fotopoulou et al., 2014). However, the Phase III study for this agent failed due to a deficit in bioavailability of the oral formulation adopted (Fotopoulou et al., 2014). Triphendiol, selected because of its better bioavailability in

animals (Saif et al., 2009; Wang et al., 2011), was subjected to one Phase Ia clinical trial in Australia. This pharmacokinetic (PK) study showed that the compound underwent extensive liver metabolism in humans, producing a demethylated metabolite (ME-143) which *in vitro* studies found to be a significantly more potent anti-cancer agent.

Commencing in 2009, Kazia Therapeutics Limited embarked on a drug discovery program seeking to achieve greater complexity of structure of its benzopyran drug technology platform. The progression in structural complexity from phenoxodiol, to triphendiol and then to ME-344 had resulted in progressive log-fold increases in anti-cancer activity. Along with that increased potency came subtle changes in the molecular target, with phenoxodiol causing caspase-dependent apoptosis, triphendiol and ME-143 causing both caspase-dependent and -independent apoptosis, and ME-344 killing cancer cells by catastrophic autophagy.

A breakthrough in manufacturing technology, allowed the creation of benzopyrans of considerably greater complexity not previously possible, resulting in a new family of compounds with a 1 to 2 log-fold increase in anti-cancer potency compared to the earlier "simple" benzopyrans such as ME-344. This increase in anti-cancer potency is believed to come from an increase in the electron-transferring potential of the molecule, with both stronger electron donating and receiving activity. Such changes are well recognised as leading to stronger drug-target interactions. TRX-E-002-1 is the first of this "superbenzopyran" family of molecules to enter clinical research.

4.1.1 Pre-Clinical Findings

Cantrixil delivers a potent anti-cancer effect in a stringent mouse model of human ovarian cancer. The model is one where human CD44+ve cells are formed into spheroids and then injected intraperitoneally into athymic mice. This is a highly aggressive model where the spheroids form detectable tumours within 4 days in a disseminated manner throughout the abdomen. There is extensive tumour load and profound ascites by Day 20 without treatment requiring sacrifice of animals. In this model, Cantrixil injected intraperitoneally daily significantly reduces carcinomatosis, whereas cisplatin therapy produces a transient response, followed by rapid tumour recurrence. The anti-tumour effect has been demonstrated at doses of 50 and 100 mg/kg administered daily and also at 150 mg/kg administered three times a week. Cantrixil is non-irritant when dosed via the intraperitoneal route in this model.

Cantrixil was also shown to be effective in a mouse model of recurrent chemotherapy-resistant ovarian cancer. In this model, mice were inoculated with human ovarian cells, tumours were allowed to establish, and the mice were then treated with standard chemotherapy (paclitaxel). While initially responding to chemotherapy, tumours

eventually recurred while still on therapy, thereby mimicking progressive chemo-resistant disease in women. In contrast to those mice treated with taxol, when mice with chemo-resistant tumours were treated with Cantrixil their growth was significantly inhibited. These data confirm that Cantrixil is active in a model of recurrent ovarian cancer where tumours are resistant to both cisplatin and paclitaxel and demonstrates the potential of Cantrixil for treating both therapy naïve and chemotherapy-resistant ovarian cancer in the clinic.

Absorption, distribution, metabolism, and excretion (ADME) studies in healthy rats indicated that after intraperitoneal administration of a single dose of Cantrixil, TRX-E-002-1 had a relatively short half-life (time to maximum plasma concentration [t_{max}] = 0.5 to 2 hours and apparent terminal half-life [$t_{1/2}$] = 2 to 3 hours) and was present in plasma and tissue predominantly in the parent, unconjugated form. High levels were observed in kidneys, pancreas, stomach, large intestine, adrenals, ovaries and skin although this was largely eliminated at 24 hours after exposure from all tissues except the large intestine. The drug was eliminated via both renal and hepatic routes in rats. A similar ADME profile was observed in dogs, except that it was cleared from the large intestine at 72 hours and while circulating TRX-E-002-1 was predominantly in the parent unconjugated form, it was conjugated in the tissues. In dogs and rats, following 14-day repeat exposure, there was no evidence indicating accumulation of TRX-E-002-1 with multiple dosing.

Escalating dose studies indicated that the maximum tolerated dose (MTD) following a single dose of Cantrixil was 50 mg/kg in male and female rats. Based on a 28-day repeat dose and 14-day recovery study, the No Observed Adverse Effect Level (NOAEL) was observed to be 3 mg/kg for male rats and 10 mg/kg for female rats and the No Effect Level (NOEL) was 0.5 mg/kg for both male and female rats.

Dogs appeared to tolerate higher doses of Cantrixil than rats, with single doses up to 80 mg/kg being administered without obvious clinical signs of toxicity. The MTD for dogs was considered to be greater than 200 mg/kg for a single dose of Cantrixil. A 28-day repeat dosing study concluded that the NOAEL for male and female dogs together was 10 mg/kg. In both species, there was a gender specificity in tolerance to Cantrixil.

In both species (i.e., rats and dogs), clinical signs included lethargy, discoloured faeces, liquid/soft faeces, soft faeces and emesis. Necropsy and histological test article-related observations were most prominently seen in the gastrointestinal (GI) tract with red streaking a common observation. These GI toxicities resolved during the 14-day recovery period. Testis toxicity was also observed in both species with an effect on spermatogenesis and these effects did not completely resolve during the 14-day recovery period. Electrocardiogram (ECG) readings in dogs showed no effect of Cantrixil on the QT interval. Mild changes in blood pressure, heart rate and body temperature were

observed immediately following dosing but these parameters returned to normal within hours of dosing.

Further information can be found in the Investigator's Brochure (IB) (Cantrixil Investigator's Brochure).

4.2 Rationale

Cantrixil is the first of this new "super" benzopyran drug family to reach the clinical research stage of development and is designed for intraperitoneal delivery. Pharmacokinetic studies have shown that intraperitoneal administration of chemotherapy results in a 10 to 20-fold higher drug exposure to tumours in the peritoneum than achieved with IV administration of chemotherapy. In addition, drugs administered to the peritoneal cavity have a significantly longer half-life than drugs given intravenously (Gourley et al., 2016). Based on the body of evidence in the literature (now 8 randomised clinical trials) (Jaaback et al., 2011), the National Cancer Institute (NCI) encourages the use of a combined IV and intraperitoneal chemotherapy regimen for ovarian cancer patients (Trimble and Alvarez 2006). Although intraperitoneal regimens resulted in higher rates of toxicity compared with IV, the evidence suggests that the benefits of intraperitoneal delivery outweigh the risk, with overall survival for women with advanced ovarian cancer extended by about 1 year (Walker 2013; Tewari et al., 2015).

The unequivocal and reproducible efficacy of Cantrixil in mouse models of ovarian cancer and the relative tolerance of Cantrixil in both rodent and non-rodent animals, warrants further development of this drug candidate. The anti-tumour effect in a mouse model has been demonstrated at doses of 50 and 100 mg/kg administered daily and also at 150 mg/kg administered three times a week. Cantrixil is non-irritant when dosed via the intraperitoneal route in this model. This Phase I study represents the next step in the clinical development program for Cantrixil. In this study, initially the drug will be delivered as a single agent in order to identify the MTD as a monotherapy. Safety and tolerability profiles of Cantrixil in humans will be investigated as well as the drug's PK profile when delivered as a single agent. Once tolerance as a monotherapy has been established, the safety of Cantrixil as part of a combination therapy with standard chemotherapy agents will be examined. An initial assessment of the potential benefits of the drug will also be examined using tumour imaging and biomarkers to assess anti-cancer activity.

The starting dose of Cantrixil of 0.24 mg/kg has been chosen based on the animal toxicology data. A common approach for many small molecules is to set the start dose at 1/10 the severely toxic dose in 10% of the animals (STD 10) in rodents (Senderowicz, 2010). In light of the good tolerance of this molecule in mice and dogs, as well as the MTDs determined in recent human clinical trials for related compounds (ME-344 and

ME-143; Bendell et al., 2014, Pant et al., 2014), the starting dose has been set at 1/10th the observed STD10 in rats. The human equivalent dose is 0.24 mg/kg, calculated using standard species conversion tables (FDA Guidance 2005) and adding a safety factor of 10. This starting dose is around ten-fold less than the starting dose in humans for ME-143 (2.5 mg/kg) and ME-344 (1.25mg/kg) (Bendell et al., 2014; Pant et al., 2014).

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal product(s) (IMPs) will meet the requirements of European Union (EU) and Food and Drug Administration (FDA) Good Manufacturing Practices (GMP).

4.3 Risk Assessment

As this is the first study of Cantrixil in humans, there is no information on its PK and metabolism, safety or efficacy in a clinical setting.

Non-clinical studies in rats and dogs have been undertaken. Some of the clinical signs observed in these studies included lethargy, swelling of the abdomen, discoloured faeces, liquid/soft faeces, and soft faeces. Necropsy and histological study drug-related observations were most prominently seen in the gastrointestinal tract and male reproductive organs. ECG readings in dogs showed no effect of Cantrixil on the QT interval.

Preliminary data from experiments in human hepatic microsomes indicate that TRX-E-002-1 may inhibit cytochrome P450 drug metabolising enzymes, including CYP2C9, CYP2C8, CYP2C19, CYP2B6, CYP3A4, CYP2D6, CYP2A6 and CYP1A2. The results suggest that caution is warranted when administering Cantrixil with drugs metabolised by cytochrome P450 enzymes until further information is available. In particular, the potential interaction between Cantrixil and paclitaxel, a CYP2C9 substrate frequently used in the treatment of ovarian cancer, needs to be considered. It should also be noted that given the toxicity observed in male reproductive organs and spermatozoa, males should initially be excluded from this Phase I study. Other study drug-related effects were predominantly associated with the gastrointestinal tract, specifically nausea, emesis and diarrhoea.

4.4 Urgent safety measures

The Sponsor and Investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken the Sponsor shall immediately (no later than 3 days from the date the measures are taken) give written notice to the licensing authority and the relevant Ethics Committee of the measures taken and the circumstances giving rise to those measures.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

5 STUDY OBJECTIVES

5.1 Primary Objectives

- To determine the 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 PK of intraperitoneal Cantrixil when delivered as a single agent and in combination with standard chemotherapy.

5.2 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.

5.3 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.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This study is a progressive design with 3 discrete Parts (Part A: Dose escalation and Part B: Dose expansion). The overall study schema is presented in Figure 1.

Cycle 1/Part A is a dose-finding assessment (dose escalation) to establish the MTD of Cantrixil when administered as a single dose once a week for 3 weeks. Cycle 2/Part A continues with 3 additional weekly doses of Cantrixil as a monotherapy before an assessment of disease response. In Cycles 3 to 8/Part A patients will be administered the same once-weekly dose of Cantrixil they tolerated in Cycles 1 and 2 (tolerance defined as no dose limiting toxicities [DLTs] or unacceptable adverse events [AEs]) in combination with a standard chemotherapy agent, in order to assess the safety and tolerability of Cantrixil in combination therapy. Standard chemotherapy drugs will be administered at the standard efficacious doses to maintain optimum benefit of known drug combinations for patients. Treating physicians may choose the combination therapy from the list in Table 1 taking into consideration factors such as pre-existing comorbidities, prior toxicities and responses as well as patient and physician preferences.

Table 1 Permitted Combination Therapies

Regimen	Reference
Carboplatin AUC 4 over 1 h on Day 4 every 21 d for six cycles	Dizon et al., 2015
Liposomal doxorubicin 40-50 mg/m ^{2} IV over 30 min on Day 4 every 21 d	Gordon et al., 2004
Gemcitabine 1000 mg/m² IV over 30 min on Days 4 and 11 (Parts A and B); every 21 d	Markman et al., 2003
Paclitaxel 80 mg/m ^{2} IV over 1 h weekly on Days 4, 11 and 18 (Parts A and B)	Markman et al., 2006
Docetaxel 75-100 mg/m ^{2} IV over 1 h on Day 4 every 21 d	Rose et al., 2003
Topotecan 4.0 mg/m^2 on Days 4, 11 and 18 every 21 d	Sehouli et al. 2011
Best supportive care and extended monotherapy with Cantrixil alone	

Combination chemotherapy may not be administered until 24 hours after administration of Cantrixil to avoid any adverse drug-drug interactions. All combination therapies and concomitant medications must be diligently recorded in the patients' electronic case report form (eCRF).

Once the MTD has been determined in Part A/Cycle 1, an additional 12 patients will be recruited in an expansion cohort for Part B. These patients will receive 2 cycles of Cantrixil monotherapy at the MTD, followed by up to 6 cycles of combination therapy.

Patients enrolled into the respective parts of the study may not receive treatments under different parts of the protocol e.g., if a patient enters Part A, she may not also continue to Part B even if she considered to have completed Part A.

To accommodate the intraperitoneal administration of Cantrixil, an in-dwelling, closed catheter or port will be inserted if the patient does not already have one. For intraperitoneal ports, the minimum period between port placement and the first administration of Cantrixil must not be shorter than 7 days. For other intraperitoneal access devices, the period may be shorter if adequate stability and/or healing of the delivery system's insertion site is confirmed by the treating physician.

Patients should begin protocol treatment within a maximum of 28 days of enrolment (i.e., signing of consent form).

Patients will start at Dose Level 0 (see Table 2) which is calculated to be the human equivalent of 10% of the STD10 dose in rats (dose is 1/10 the severely toxic dose in 10% of rats tested). Single patient cohorts will be treated with increasing doses of Cantrixil until an AE is observed during Part A/Cycle 1 that meets the definition of a DLT or, in the opinion of the Data Safety Monitoring Committee/Board (DSMC/B) and the Investigator, warrants observing additional patients at this dose level; at this point the study will revert to a 3+3 rules-based dose escalation study (see Section 6.1.2). The decision to expand from single patient cohorts to 3 patient cohorts is critical for the safety of participants and will be made with input from the Investigator and DSMC/B responsible for this study (see Section 6.1.1). Dose levels -1 and -2 will only be activated if there are 2 DLTs at Dose Level 0 and -1, respectively. Once the study enters a 3+3 rules-based design, the study will not revert back to single patient cohorts.

Table 2 Doses at each Dose Level

Dose Level	Cantrixil	Patient Number
Level -2	0.06 mg/kg Dose is half of Level -1	n = 2 to 6
Level -1	0.12 mg/kg Dose is half of Level 0	n = 2 to 6
Starting dose: Level 0	0.24 mg/kg Dose is equivalent to 10% of STD10	n = 1 to 6
Level 1	0.6 mg/kg Dose is 2.5 x Dose Level 0	n = 1 to 6
Level 2	1.25 mg/kg Dose is 2.1 x Dose Level 1	n = 1 to 6
Level 3	2.5 mg/kg Dose is 2 x Dose Level 2	n = 1 to 6
Level 4	5.0 mg/kg Dose is 2 x Dose Level 3	n = 1 to 6
Level 5	10.0 mg/kg Dose is 2 x Dose Level 4	n = 1 to 6

Level 6	20.0 mg/kg Maximum dose to test	n = 1 to 6

STD10: Severely toxic dose in 10% of rats tested

If any of the following unacceptable AEs or DLTs are observed and unless clearly unrelated to study treatment (e.g., disease progression), treatment at the currently allocated Cantrixil dose will be be paused. At this point a dose reduction may be considered or the treatment may be terminated, depending on what is considered by the investigator to be in the participant's best interest.

- Hematologic toxicity
    - Grade 4 neutropenia, lasting at least 5 days,
    - Grade 3 or Grade 4 neutropenia associated with fever >38.5°C,
    - Grade 4 thrombocytopenia lasting at least 5 days,
    - Grade 3 thrombocytopenia associated with severe bleeding in the opinion of the Investigator,
    - Dose delay of ≥3 weeks due to failure to recover counts.
- Any Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Grade 3 or Grade 4 non-haematological toxicity except:
    - Alopecia,
    - Grade 3 abdominal pain deemed related to the port or catheter as determined by the treating physician,
    - Grade 3 anorexia,
    - Grade 3 fatigue,
    - Grade 3 nausea and/or vomiting, or diarrhoea, lasting ≤48 hours with or without maximal medical management,
    - Grade 3 dehydration as a result of nausea and vomiting,
    - Grade 3 constipation,
    - Grade 3 metabolic abnormalities [hypokalaemia, hypomagnesemia, hypocalcaemia, hypophosphatemia]) that recovers to Grade 1 or less within 48 hours with or without medical management,
- Other serious adverse events which, in the opinion of the treating investigator, necessitate temporary or permanent cessation of administration,
- Treatment delays of ≥3 weeks due to any non-haematological toxicity will constitute a DLT.

If any unacceptable AE or DLT is observed in any cycle, patients may be dose reduced to the next lower dose level of Cantrixil for subsequent doses of therapy. If a second unacceptable AE or DLT is observed during any cycle within the same patient, treatment with Cantrixil will be discontinued. Investigators may continue with the standard chemotherapy at their discretion and if it is considered safe and in the patient's best interest.

All patients who discontinue from the study treatment (i.e. are now Off Therapy/End of Therapy) will progress to follow-up unless the patient withdraws consent.

The initiation of each new cycle of Cantrixil will be at the discretion of the Investigator and will depend on the potential or measurable benefit to the patient assuming continued tolerability and adequate organ function.

Cantrixil treatment will also be stopped due to RECIST version 1.1 defined disease progression observed after at least 2 cycles of combination therapy, or patient consent withdrawal. Note that patients with progressive disease at the end of 2 cycles of Cantrixil monotherapy will not be taken off therapy if Cantrixil has been well-tolerated. Pre-clinical data would suggest that the maximum benefit of Cantrixil will be realised as a combination therapy, hence all patients will have the opportunity to continue receiving Cantrixil as a combination therapy. Additionally, patients receiving combination therapy that are observed to have progressive disease as identified by RECIST version 1.1 criteria but who, in the opinion of the Investigator, continue to derive clinical benefit, may continue treatment. Patients may also be discontinued from study treatment if the Investigator considers continuing therapy is not in the patient's best interest.

All patients discontinued from study treatment (i.e. are now Off Therapy/End of Therapy) will progress to follow-up unless the patient withdraws consent.

Tumour assessment via radiological imaging will be conducted during screening and every 6 weeks, i.e., at the end of monotherapy and then after every 2 cycles of combination therapy. The screening period is up to 28 days before the Cycle 1 Day 1 dose of Cantrixil. Either contrast-enhanced magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) may be used, but once a modality is used at baseline this must be used consistently for that patient throughout their participation on the study. Other imaging is not mandatory, but may be performed if clinically indicated.

Adverse events will be monitored for the duration of the study from the time of informed consent. Blood samples will be collected weekly for standard safety testing, or more frequently if clinically relevant, during the study. Additional volumes of blood will be collected before and after administration of Cantrixil for PK analysis (4 mL per time point as per the proposed PK schedule [Table 5] and for any exploratory studies (at baseline, end of Cycles 2, and End of Therapy - 15 to 20 mL at each time-point).

Part A (Dose escalation of Cantrixil as a monotherapy):

Cycle 1

Following placement of a port or catheter, eligible patients will be administered a single intraperitoneal dose of the study treatment Cantrixil (TRX-E-002-1 formulated in Dexolve-7) once a week for 3 weeks. Patients will be monitored for DLTs over the 21-day cycle (Cycle 1).

Blood samples will be collected weekly at each scheduled visit for standard safety testing, or more frequently if clinically relevant. Results of the safety assessments must be available prior to Cantrixil administration to ensure that all assessments still meet the inclusion criteria as described in Section 6.2.1 and it is safe to proceed to the next dose of treatment. Treatment delays of up to three weeks are allowed for recovery without being classified as a protocol deviation or a dose limiting toxicity.

Patients will continue to be monitored until they meet the off-study criteria (see below) but will only be evaluable for DLTs that define the MTD of Cantrixil as a monotherapy during Cycle 1/Part A.

Patients will start at Dose Level 0 (see Table 2) which is calculated to be the human equivalent of 10% of the STD10 dose in rats (dose is 1/10 the severely toxic dose in 10% of rats tested). Single patient cohorts will be treated with increasing doses of Cantrixil until an AE is observed during Part A/Cycle 1 that meets the definition of a DLT or, in the opinion of the DSMC/B and the Investigator, warrants observing additional patients at this dose level; at this point the study will revert to a 3+3 rules-based dose escalation study (see Section 6.1.2). The decision to expand from single patient cohorts to 3 patient cohorts is critical for the safety of participants and will be made with input from the Investigator and DSMC/B responsible for this study (see Section 6.1.1). Dose levels -1 and -2 will only be activated if there are 2 DLTs at Dose Level 0 and -1, respectively.

Cycle 2

Patients that are still on study treatment at the end of Cycle 1/Part A will receive another cycle of Cantrixil monotherapy with once weekly dosing before disease assessment. Note that a disease assessment will be conducted at the end of monotherapy but patients will not automatically be removed from therapy at this time-point if they have progressive disease as defined by RECIST version 1.1 criteria. This is because the pre-clinical data strongly suggests that the benefit of Cantrixil will most likely be realised as a combination therapy. All patients will, therefore, have the opportunity to progress to a combination therapy with Cantrixil.

Patients that have not discontinued from the study at the end of Cycle 2 will proceed to Cycles 3 to 8/Part A of the study.

Cycles 3 to 8 (Cantrixil in Combination with Standard Chemotherapy)

Patients that progress to Cycles 3 to 8/Part A will continue on the same dose level of Cantrixil that they tolerated in Cycles 1 and 2/Part A but in combination with a systemic chemotherapy selected from Table 1 for the patient by the treating physician/Investigator. In the rare event that there does not exist a combination chemotherapy that could be recommended by the Investigator, patients may continue to Cycles 3 to 8 receiving Cantrixil as a monotherapy if it is deemed by the Investigator and the patient to be providing potential benefit as a monotherapy.

During Cycles 3 to 8/Part A, patients will be administered Cantrixil once per week for each 21-day cycle. The combination chemotherapy will be administered as per the schedules in Table 1. Before administration of the combination chemotherapy, the PK results for each patient from Part A/ Cycle 1 will be reviewed by the DSMC to ensure that the PK profile of Cantrixil is indeed compatible with the proposed schedule for the combination chemotherapy agent.

With the anticipated PK profile of Cantrixil, there should be a 24-hour window after each dose of Cantrixil before any other chemotherapy agent is administered to avoid any drug-drug interactions. All combination therapies and concomitant medications must be diligently recorded in the patient's eCRF.

Part B (Expansion Cohort at MTD):

Once the MTD has been established in Part A/Cycle 1, an expansion cohort will be recruited at the MTD. An additional 12 patients will be recruited in this cohort on top of those recruited in Part A at the MTD. These patients will be subjected to the same intervention described above with 2 cycles of monotherapy followed by up to 6 cycles of combination therapy.

Continued Access for Patients:

All patients who complete eight cycles, and in whom the local Investigator feels there has been a clinical benefit from treatment, may continue to receive Cantrixil, following discussion with the Sponsor. Those patients granted continued access will be dosed weekly with Cantrixil at the dose that they have been receiving during cycles 1 to 8. Patients will be monitored and supported as per local standard of care procedures, including any blood and urine safety assessments and on-going radiology assessments. During this period of extended access, Kazia will only collect data on adverse events, Cantrixil administration and drug accountability. Cantrixil treatment will be stopped due to locally defined disease progression, recurrence of an unacceptable toxicity after 1 Cantrixil dose reduction or patient consent withdrawal. The definition of unacceptable toxicity during this extended access period is the same as defined in section 6.1.3. Patients may also be discontinued from study treatment if the Investigator considers

continuing therapy is not in the patient's best interest. When dosing of Cantrixil is discontinued, the Off Therapy/End of Therapy schedule of assessments in Table 4 should be conducted. All patients discontinued from study treatment (i.e. are now Off Therapy/ End of Therapy) will progress to follow-up unless the patient withdraws consent.

It is at the discretion of the Investigator whether this continued treatment is a maintenance monotherapy or a combination chemotherapy.

All patients that are provided continued access to Cantrixil must agree to on-going data collection for monitoring safety, progression and survival.

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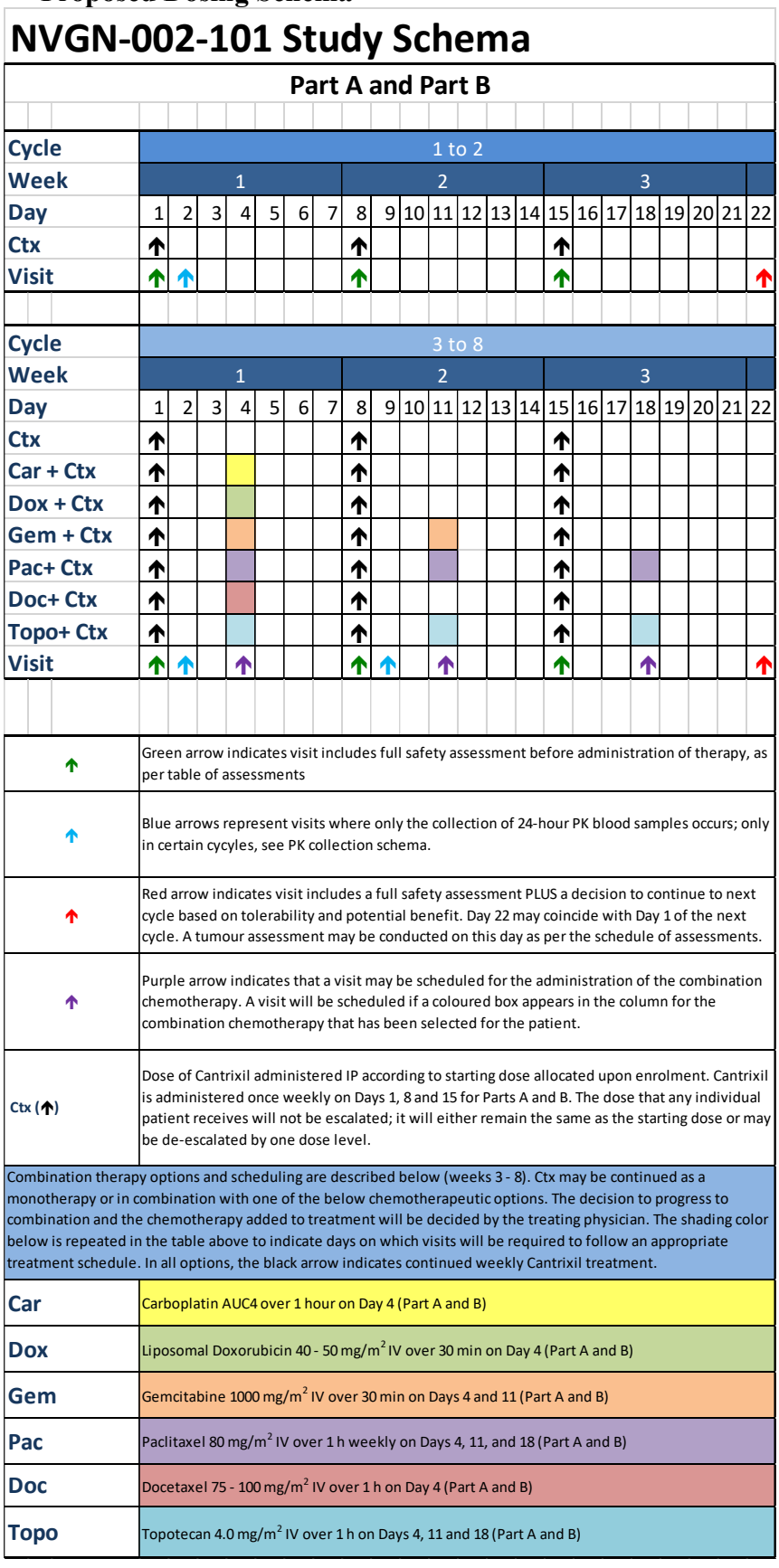
Figure 1 Proposed Dosing Schema



6.1.1 Data Safety Monitoring Committee/Board

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 DSMC/B will review safety data from each patient at the end of each Part A/Cycle 1 to confirm that it is safe to dose escalate and to assess the compatibility of the proposed combination therapy schedule. Written confirmation from the DSMC/B will be required before a patient can be administered a higher dose than the previously enrolled patient or proceed to combination therapy.

An appropriate interval will separate the investigation of dose levels to permit a timely review and evaluation of safety, tolerability and PK data prior to proceeding to a higher dose level.

All data reviewed at the DSMC/B meeting (safety, tolerability and PK where appropriate) will be subjected to a quality control (QC) review.

The DSMC/B will continue to assess safety data throughout the course of the study, and may discontinue patient exposure to particular combinations if evidence of unacceptable toxicity emerges.

6.1.2 Dose Escalation Criteria

Single patient cohorts will be treated with increasing doses of Cantrixil until a treated patient exhibits an AE during Part A/Cycle 1 that meets the definition of a DLT or, in the opinion of the Investigator and the DSMC/B, warrants observing additional patients at this dose level; at this point the study will revert to a 3+3 rules-based dose escalation design (see Table 3). During the single patient cohort stages and the 3+3 design, once the single patient or the first 3 patients at a dose level have completed Cycle 1/Part A, tolerability data will be evaluated by the DSMC/B and a decision to escalate to the next dose level will be made. Once the study enters a 3+3 rules-based design, the study will not revert back to single patient cohorts.

Table 3 3+3 Design Dose-escalation Plan

Number of patients with DLT at a given dose level	Action
0 out of 3	Enter at least 3 patients at the next dose level.
1 out of 3	Enter at least 3 more patients at this dose level and • *if 0 of these 3 new patients experiences a DLT*, proceed to the next dose level; • *if ≥1 of this group suffer a DLT (for a total of ≥2/6 patients with a DLT)*, this dose exceeds the MTD and dose escalation is stopped. To further assess tolerability, 3 additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. Upon determination of the MTD, the study will proceed to Part B of the study.
≥2	Dose escalation will be stopped. This dose exceeds the MTD. To further assess tolerability, 3 additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose and the study will proceed to Part B of the study.

DLT: Dose limiting toxicity; MTD: maximum tolerated dose

Progression to the next higher dose level will be stopped if one or more patients experience a DLT (as outlined in Table 3) but also if an AE occurs that, in the opinion of the Investigator or Sponsor's medical representative and the DSMC/B, warrants discontinuation of dose escalation.

6.1.3 Study Stopping Rules

Dosing for any individual patient will be stopped if the patient experiences a SAE or an AE, which in the opinion of the Investigator or Sponsor's medical representative or DSMC/B, warrants discontinuation of the study treatment for that patient's wellbeing.

If any of the following unacceptable AEs or DLTs are observed and unless clearly unrelated to study treatment (e.g., disease progression), treatment at the currently allocated Cantrixil dose will be paused. At this point a dose reduction may be considered or the treatment may be terminated, depending on what is considered by the investigator to be in the participant's best interest.:

- Hematologic toxicity
    - Grade 4 neutropenia, lasting at least 5 days,
    - Grade 3 or Grade 4 neutropenia associated with fever >38.5°C,
    - Grade 4 thrombocytopenia lasting at least 5 days,

- Grade 3 thrombocytopenia associated with severe bleeding in the opinion of the Investigator,
- Dose delay of ≥3 weeks due to failure to recover counts to levels described in the study inclusion criteria as described in Section 6.2.1.

- Any CTCAE version 4.03 Grade 3 or Grade 4 non-haematological toxicity except:
  - Alopecia,
  - Grade 3 abdominal pain deemed related to the port or catheter as determined by the treating physician,
  - Grade 3 anorexia,
  - Grade 3 fatigue,
  - Grade 3 nausea and/or vomiting, or diarrhoea, lasting ≤48 hours with or without maximal medical management,
  - Grade 3 dehydration because of nausea and vomiting,
  - Grade 3 constipation,
  - Grade 3 metabolic abnormalities [hypokalaemia, hypomagnesemia, hypocalcaemia, hypophosphatemia]) that recovers to Grade 1 or less within 48 hours with or without medical management,
- Other serious adverse events which, in the opinion of the treating investigator, necessitate temporary or permanent cessation of administration,
- Treatment delays of ≥3 weeks due to any non-haematological toxicity will constitute a DLT.

All patients who discontinue from the study treatment (i.e. are now Off Therapy/End of Therapy will progress to follow-up unless the patient withdraws consent.

The occurrence of significant safety events as described above will require that further dosing of other patients be evaluated by the Investigator or Sponsor's medical representative to determine study discontinuation.

6.1.4 Discussion of Study Design

Current literature on Phase I dose-escalation designs suggests that when the pre-clinical data indicate a wide therapeutic window and little expected toxicity in human patients, it is very reasonable to apply an aggressive dose titration (e.g., by using an accelerated titration design or Bayesian-based methods) (Le Tourneau et al., 2009). However, if the pre-clinical data were less certain about how human patients will tolerate the drug or predict a very narrow therapeutic window, then it would be prudent to choose a more

conservative dose escalation scheme (Le Tourneau et al., 2009). Given the good tolerability of this class of drugs in humans as demonstrated in the clinical trials using Phenoxodiol, ME-143 and ME-344 (Saif et al., 2009, Pant et al., 2014) and the excellent tolerability of Cantrixil in mice and dogs, this study will adopt a dose escalation scheme that is accelerated compared to the traditional Fibonacci sequence but starts at the conservative 10% of STD10 level.

6.2 Study Population

Patients with any stage of persistent or recurrent ovarian cancer, fallopian tube cancer or primary peritoneal cancer will be enrolled into this study provided that they satisfy the following inclusion/exclusion criteria.

6.2.1 Subject Inclusion Criteria

For inclusion in the study, patients have to fulfil all of the following criteria:

1. Patients must have recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer. The original diagnosis must be verified by a histology report. All histological sub-types and all grades of disease are eligible to participate; grade, histological sub-type and breast cancer susceptibility gene (BRCA) status must be recorded at study entry.
2. Patients must be female and at least 18 years old. Patients may be women of child-bearing potential as long as they are not pregnant or breast-feeding and able to adopt adequate contraception as described in section 6.2.3.1
3. Patients with malignant ascites are eligible to participate; paracentesis will be conducted before the administration of Cantrixil. Drainage of the maximum volume of ascites should be performed according to local standard operating procedures before administration of Cantrixil.
4. Patients must have completed at least two (2) or more prior regimens (including adjuvant therapy) for their ovarian, Fallopian tube or primary peritoneal cancer prior to participation in the current study; all prior therapies must be recorded at baseline. Patients that have received prior intraperitoneal therapy are eligible for this study. Patients should have failed standard of care drugs prior to being eligible to be part of the proposed study.
5. Patients must have platinum-resistant relapsed disease, platinum refractory disease, or have documented intolerance to platinum therapy. Patients will not be eligible based on rising CA-125 levels alone, patients must have other clinical symptoms (such as malignant ascites) or radiological tumour measurements that support disease recurrence or progression.

6. At least 4 weeks must have passed from any previous therapy (6 weeks for bevacizumab, nitrosoureas or mitomycin C treatment) any toxicities from prior therapies must have resolved to less than or equal to CTCAE version 4.03 Grade 1 with the exception of alopecia, Grade 2 prior platinum-therapy related neuropathy and Grade 2 anaemia.
7. Patients must have a performance status of Eastern Cooperative Oncology Group (ECOG) 0 to 2 and, in the Investigator's opinion, be able to complete at least a major part of the study.
8. Patients willing and able to undergo insertion of a port or catheter for intraperitoneal access; the type of port or catheter used will be at the discretion of the Investigator and will be recorded.
9. Patients with measurable or non-measurable disease may be enrolled; disease response will be measured according to RECIST version 1.1 criteria using contrast CT or MRI and CA-125 measurements.
10. Patients with acceptable hepatic and marrow function as defined below:
    - Absolute neutrophil count $\geq$1.5 x 10^9/L without myeloid growth factor support.
    - Platelets $\geq$100 x 10^9/L.
    - Total bilirubin; <2.5 times the institutional upper limit of normal (ULN).
    - Haemoglobin (Hb) of >10 g/dL; patients with Hb >9g/dL will be considered for this study if they have not received a transfusion or other bone marrow support. Patients with Hb >10 g/dL that have received a recent transfusion will only be eligible if there has been a wash-out period of 7 days for rhesus factor and 10 days for platelet transfusions, respectively.
    - Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT])/ alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase [SGPT]) $\leq$2.5 x institutional ULN if no demonstrable liver metastases or <5 x ULN in the presence of liver metastases.
    - Serum creatinine <1.5 x ULN.
    - Prothrombin time (PT) or international normalised ratio (INR) $\leq$1.5 x ULN and activated partial thromboplastin time (aPTT) $\leq$1.5 x ULN if not on anticoagulation treatment.

11. Patients willing and able to comply with all study requirements, including treatment timing and/or nature of required assessments and treatment at designated study centre.
12. Each participant must be adequately informed about the purpose of the study; potential benefits and risks; their right to refuse participation or to withdraw consent at any time; institutional affiliation and potential competing interests of the researcher; and sources of study funding and have signed and dated a written informed consent form.

6.2.2 Subject Exclusion Criteria

Any of the following is to be regarded as a criterion for exclusion from the study:

1. Patients who have had chemotherapy, targeted therapies, biologic therapy, immunotherapy, or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C or bevacizumab) prior to entering the study.
2. Patients must not have had major surgery within 4 weeks prior to screening.
3. Patients may not have received any other investigational medicinal products (IMPs) or participated in any other interventional clinical research studies within 4 weeks of the first Cantrixil administration.
4. Patients receiving any medications or substances that are strong inhibitors or inducers of cytochrome P450 (CYP)1A2, CYP2B6 and CYP3A4 or those substances with narrow therapeutic index are not to be enrolled. These compounds are prohibited from screening until completion of end of therapy or first post-treatment follow-up visit. For a list of prohibited medications see the University of Indiana Clinical Pharmacology Department's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/). Note: the use of paclitaxel is allowed, but only 24 hours after Cantrixil administration.
5. Patients deemed by the investigator to be at high risk of bowel perforation or obstruction are excluded, including but not limited to any one or more of the following;
    - Patients with a recent history (previous 12 months) of bowel obstruction prior to study entry.
    - Patients with CT scans that suggest invasion of bowel by tumour.
    - Patients with symptoms to suggest impending bowel obstruction.
    - Patients with prior whole abdominal radiotherapy.

- Patients with chronic inflammatory bowel diseases such as Crohn's disease or ulcerative colitis.

6. Patients may not have uncontrolled or severe systemic diseases or psychiatric conditions, which in the Investigator's opinion makes it unsafe for the patient to participate in the study or would hinder compliance with the protocol. Screening for chronic conditions is not required.
7. Patients who are pregnant, lactating, or unable to adopt adequate contraception; women of childbearing potential must have a negative pregnancy test within 7 days prior to screening.
8. Patients with active hepatitis B or C.
9. Patients known to have tested positive for human immunodeficiency virus (HIV).
10. Patients with a known hypersensitivity to or a serious reaction to benzopyrans are excluded.

6.2.3 Restrictions

- All medications, both prescription and over-the-counter (OTC), taken within 30 days of the study screening must be reported and recorded on the eCRF.
- Grapefruit and grapefruit juice are prohibited, from 1 week prior to the start of the study (Day 1) until the last PK sample has been collected.
- Use of medications or substances that are strong inhibitors or inducers of cytochrome P450 (CYP)1A2, CYP2B6 and CYP3A4 or those substances with narrow therapeutic index are prohibited from screening until completion of end of therapy or first post-treatment follow-up visit. For a list of prohibited medications see the University of Indiana Clinical Pharmacology Department's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/). Note: the use of paclitaxel is allowed, but only 24 hours after Cantrixil administration.
- Medications which are moderate to weak P450 enzyme inducers or inhibitors (see list referenced above), should have a complete washout prior to Cantrixil administration and only be administered 24 hours after Cantrixil administration. These medications should be used with caution and the Investigator should be alert for any potential unpredictable drug-drug interactions.

6.2.3.1 Avoidance of Pregnancy

Women of Childbearing Potential

Pregnancy should be avoided by either true abstinence or the use two effective means of contraception (see Section 6.2.3.2) for the duration of the study and a total period of 3 months after the patient has taken the last dose of Cantrixil.

In order to include women of childbearing potential in any clinical trial, certain precautions pertaining to pregnancy must be taken. These will include pregnancy testing at screening, at the start of each cycle, and follow-up.

Female patients who become pregnant during the study will be withdrawn.

Women of Non-Childbearing Potential

Female patients of non-childbearing potential are defined as; no menses for 12 months without an alternative medical cause, a hysterectomy within the last 12 months, bilateral tubal occlusion/ligation and bilateral oophorectomy. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

6.2.3.2 Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

Acceptable forms of effective contraception are:

- Combined oestrogen and progestogen containing hormonal contraception (oral, intravaginal or transdermal) associated with inhibition of ovulation.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomised male partner should be the sole partner for that patient.
- True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal,

post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
  - Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.
  - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

6.2.3.3 Time Period for the Collection of Pregnancy Information

All pregnancies in female patients receiving at least one dose of Cantrixil will be recorded from first dose to 3 months after the final dose.

6.2.3.4 Follow-up in the Event of a Pregnancy

If a female patient becomes pregnant, the pregnancy will be recorded and reported to the Sponsor within the same timeframe as SAEs (see Section 8.3.2). The Ethics Committee and the Sponsor will be informed. The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise.

Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

The follow-up period will be deemed to have ended when the health status of the child has been determined on his/her birth.

6.2.4 Subject Withdrawals

The Investigator will make every reasonable attempt to ensure that all patients complete the study. A patient may withdraw at any time for any reason. The Investigator will advise the Sponsor of the withdrawal of any patient.

A patient may be withdrawn in any of the following circumstances:

- Adverse event(s),

- Protocol violation,
- Recurrence of an unacceptable AE or DLT despite a Cantrixil dose level reduction,
- Withdrawal of consent,
- Termination of the study by the Investigator or Sponsor,
- Completion of planned treatment and follow-up period.

Patients who voluntarily withdraw are termed dropouts.

Every effort will be made to complete all examinations scheduled on all patients who participate in the study, but do not complete the study according to the protocol. The Investigator will make every effort to contact patients lost to follow-up.

Follow-up will continue for any patient with an ongoing AE at the time of study completion until the event resolves, or until the Sponsor and the Investigator agree that further follow-up is not necessary.

7 STUDY TREATMENT

7.1 Investigational Product(s)

Cantrixil is manufactured as a clear solution for infusion (200 mg). One 10 mL glass vial (type I glass, siliconized) with plunger stopper (Westar® Flurotec stoppers) contains 10 mL of 20 mg/mL of the Active Pharmaceutical Ingredient (API) (TRX-E-002-1) in 20% Dexolve-7. Before administration, Cantrixil concentrate solution for infusion is diluted in sodium chloride 9 mg/mL (0.9%).

Stability studies are ongoing and the expiration date of the supplied vials may be updated during the course of the study as further stability information is available. After dilution, Cantrixil for infusion is stable for 24 hours at 2°C to 8°C. To prevent microbial contamination, the dilution should be used immediately after preparation. For more information on the formulation of Cantrixil, refer to the IB.

7.1.1 Supply, Packaging and Labelling

Cantrixil will be supplied to the study centre by Kazia Therapeutics Limited.

A clinical trial agreement between the study centre and Sponsor will be in place to cover all study related activities, prior to receipt of Cantrixil at the study centre.

7.1.2 Storage and Handling Procedures

Cantrixil must be stored in the original packaging protected from light in a refrigerator (2°C to 8°C). Do not freeze. All Cantrixil will be stored in the storage area of the study centre pharmacy, which is a secure, temperature controlled, locked environment with restricted access.

Cantrixil should only be prepared by a pharmacist or healthcare professional trained in the handling of cytotoxic drugs.

7.1.3 Accountability

In accordance with Good Clinical Practice, the study centre will account for all supplies of Cantrixil. Details of receipt, storage, assembly and return will be recorded.

All unused supplies of Cantrixil will either be destroyed by the study centre or returned to the study Sponsor at the end of the study in accordance with instruction by the Sponsor. If the Sponsor authorises destruction at the study centre, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided. Certificates of destruction must be completed and sent to the Sponsor.

7.2 Dosage and Administration

Dilution Instructions

Cantrixil should be prepared by a pharmacist or healthcare professional trained in the handling of cytotoxic drugs and aseptic technique must be used; ideally an aseptic suite will be used to prepare Cantrixil for administration. The outer surface of the vial is not sterile.

- Based on the dose, the appropriate amount of air is extracted into an appropriately sized syringe and needle.
- An additional air buffer should be included in the syringe.
- The plastic lid from the Cantrixil pre-filled vial is removed.
- The syringe needle is inserted through the rubber stopper of the vial being careful not to core the rubber stopper.
- The appropriate volume of the vial (Cantrixil concentrate plus air buffer) is extracted from the vial into the syringe; this process may need to be repeated if multiple vials are required to achieve the necessary volume of drug.
- The syringe and needle is shaken gently to eliminate any air bubble(s) from the syringe.
- Eject the entire contents of the syringe into a sterile bag of saline for infusion to result in a total volume of 100 mL of fluid for infusion. Note that if a patient weighs more than 100kg then more than 100mL of undiluted Cantrixil would be required to dose at 20mg/kg. Please contact the IQVIA CRA for instructions under these circumstances.
- The plunger rod MUST NOT be drawn back to rinse the syringe, in order to avoid contamination and to ensure that the correct volume is ejected.
- The peelable sticker, which is provided on the inner side of the Cantrixil carton box, displaying the text “Intraperitoneal use only.” must be attached to the saline infusion pack containing the diluted Cantrixil solution for intraperitoneal infusion. This is a precautionary measure to ensure that Cantrixil is infused only via the intraperitoneal route of administration.

Method of administration

Cantrixil must be administered via the intraperitoneal route only; an in-line filter must be part of the infusion set. The Cantrixil solution should be warmed before administration. Once warm, the infusion bag should be hung and the drug allowed to infuse under gravity flow. Subsequent to each Cantrixil administration up to 1 L of warmed sodium chloride,

9 mg/mL (0.9%) solution for injection shall be infused to support distribution of the Cantrixil solution in the abdominal cavity.

Delivery of Cantrixil and combination chemotherapy

All patients will have catheters/ports inserted to facilitate intraperitoneal chemotherapy administration. This intervention should be scheduled to occur as soon as possible after enrolment. All ports/catheters will be inserted by an interventional radiologist or surgeon and checked for patency and leakage. Patients will be referred to the interventional radiologist or surgeon by their treating oncologist. For intraperitoneal ports, the minimum period between port placement and the first administration of Cantrixil must not be shorter than 7 days. For other intraperitoneal access devices, the period may be shorter if adequate stability and/or healing of the delivery system's insertion site is confirmed by the treating physician.

Insertion of the intraperitoneal port/catheter and intraperitoneal administration of Cantrixil and standard chemotherapy will be done in accordance to each study centre's Standard Operating Procedures and guidelines, or the recommended guidelines listed in Appendix B.

The exact time that the intraperitoneal infusion has completed must be recorded.

Cycles 3 to 8 of Parts A and B of the study will include Cantrixil in combination with a standard chemotherapy agent selected for the patient from Table 1 by the treating physician/ Investigator. Standard therapies will be administered according to the schedules listed in Table 1 and recorded appropriately in the patient medical record and study eCRFs. Before administration of the combination chemotherapy, the PK results for each patient from Part A/ Cycle 1 will be reviewed by the DSMC to ensure that the PK profile of Cantrixil is indeed compatible with the proposed schedule for the combination chemotherapy agent.

With the anticipated PK profile of Cantrixil, combination chemotherapy agents should not be administered within 24 hours of Cantrixil dosing to avoid any adverse drug-drug interactions.

Cycles of Cantrixil and the combined chemotherapy may continue until the patient fulfils any of the off-therapy criteria, as described in Section 6.1. It is recommended that the catheter/port remains in the abdominal cavity during the entire treatment period. If a catheter is used it is to be kept closed between infusions.

7.3 Treatment Strategy

The clinical staff at the study centre are all responsible for the ongoing safety and well-being of the subjects while they are in the study centre.

As this is the first time that Cantrixil is being administered to patients, the study centre should be equipped with the necessary facilities to enable staff to manage potentially life-threatening events. There should be a paging system to alert the clinical staff to any area in the study centre where a patient may need medical attention. In the case of an emergency, cardiac resuscitation trolleys are to be found in the main ward areas of the study centre. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc., together with oxygen cylinders and portable suction machines. There is to be a physician on site 24 hours a day. In addition, if necessary the clinical staff can contact further on-call physicians or public emergencies services, including the ambulance and hospital resuscitation team, in the event of a serious medical event. Equipment and emergency drugs are to be available to treat common medical emergencies that might occur in a Phase I study at the study centre.

7.4 Warnings and Precautions

As this is the first administration of Cantrixil to humans, all effects cannot be reliably predicted. The pre-clinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies must be provided.

7.5 Prior and Concomitant Medication

In the interests of patient safety and acceptable standards of medical care the Investigator will be permitted to prescribe supportive care treatment(s) at his/her discretion. Palliative radiotherapy is permitted on this study but not within the peritoneum and also not during MTD cycle (Cycle 1). All treatments must be recorded in the patients' eCRF (medication, dose, treatment duration and indication).

As TRX-E-002-1, the active ingredient of Cantrixil, may inhibit CYP450 drug metabolising enzymes, including CYP2C9, CYP2C8, CYP2C19, CYP2B6, CYP3A4, CYP2D6, CYP2A6 and CYP1A2, caution should be taken when administering drugs that are metabolised by CYP450 enzymes until further information is available. In particular, the potential interaction between TRX-E-002-1 and paclitaxel, a CYP2C9 substrate frequently used in the treatment of ovarian cancer, needs to be considered. As such the use of paclitaxel is allowed, but only 24 hours after Cantrixil administration.

7.6 Method of Assigning Subjects to Treatment Groups

At screening, potential study patients will be assigned a screening number. The screening number will be prefixed with SCR. Following confirmation of eligibility, at study treatment administration, patients will be assigned a patient number in the order in which they are enrolled in the study.

If applicable, replacement patients will receive the same treatment allocation as those whom they replace.

Patients who are replaced will be allocated the same treatment number prefixed with the number 1 e.g. if treatment number 009 is replaced then the replacement number will be 109.

7.7 Randomisation Procedures (Not applicable)

7.8 Maintenance of Randomisation Codes (Not applicable)

7.9 Blinding (Not applicable)

8 STUDY PROCEDURES

Study assessments and procedures to be performed during the study are detailed in the Schedule of Assessments, Section 16; Table 4. All visits during treatment cycles 1 to 8 have a window of +/- 1 calendar day. During follow-up, the window is extended to +/- 1 week. The screening period is up to 28 days before the Cycle 1 Day 1 dose of Cantrixil.

8.1 Pharmacokinetic Assessments

Plasma Samples

Pharmacokinetic studies will be performed on all patients. At each of the sampling periods a blood sample will be collected into a 4mL dipotassium EDTA tube and the sample processed to plasma. The plasma samples will be divided into a primary and back-up sample and stored frozen at -80°C. The primary sample will subsequently be shipped to the bioanalytical laboratory. The results of the PK analysis will not be made available to the Principal Investigator, Investigators or any study centre staff during the study. The results will be made available to the DSMC/B for the purposes of patient safety. Blood sample collection times are included in the Schedule of Assessments (see Section 16).

Bioanalysis

All bioanalytical procedures will be performed by TetraQ (The University of Queensland, Brisbane, Queensland, Australia), according to their internal quality assurance protocols and procedures. Concentrations of TRX-E-002-1 in plasma will be determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) based assay. If one or more of the major active metabolites of TRX-E-002-1 is known to contribute at least 10% of the activity or toxicity observed, the PK of that/those metabolite(s) will also be measured. Full details of the bioanalytical analysis will be included separately in the Bioanalytical Report.

8.2 Efficacy Assessments

The following efficacy assessments will be measured (sample collection times are included in the Schedule of Assessments [see Section 16]):

- PFS will be measured as the time from treatment starts until objective tumour progression as defined by RECIST version 1.1 criteria or GCIG criteria (see Appendix C).
- The time to paracentesis will be measured as the time from treatment begin until the next paracentesis event.

- The volume of paracentesis will be measured by estimating the volume of malignant ascites drained at each event.
- Disease response will be measured using RECIST version 1.1 criteria; the Gynecological Cancer Intergroup (GCIG) response criteria (described in Rustin *et al*., 2011), which incorporates RECIST 1.1 and CA-125 measurements, may also be used to define disease response during Follow-up. Although the GCIG response criteria incorporating CA-125 measurements has been used successfully in clinical trials for recurrent ovarian cancer (Alexandre et al., 2012), patients are not evaluable for CA-125 if there has been a surgical or medical interference with their peritoneum during the past 28 days. Only the baseline and Follow-up measurements of CA-125, therefore, may be reliably used for determining response and progression in this study. During Follow-up, the GCIG criteria, summarised in Appendix C, may be used to define response and progression.
- Concentration of CA-125 in peripheral blood will be assayed in local hospital laboratories at baseline using locally validated assays at baseline and then weekly during treatment, at the End of Treatment and during Follow-up. These measurements may not be used to determine progression or disease response until 28 days after the last IP chemotherapy administration.

The following exploratory endpoints will also be assessed:

- 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 for patients in Part A of the study only.
- 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 for patients in Part A of the study only.
- 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.
- Efficacy of twice weekly doses of Cantrixil as a monotherapy and combination therapy.

These exploratory endpoints, if assessed, will be reported separately from the Clinical Study Report.

8.3 Safety Assessments

8.3.1 Adverse Events

Definitions:

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any clinically significant sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Patients will be followed for 3 months after discontinuing therapy or until death, whichever occurs first. Patients removed from study for unacceptable AEs will be followed until resolution or stabilisation of the AE.

Note that for this study, disease progression will not be defined as an adverse event. Disease progression will be recorded as a participant outcome but not recorded on the adverse event log.

Adverse Drug Reaction (ADR)

Any untoward and unintended response in a patient to an investigational medicinal product which is related to any dose administered to that patient.

Serious Adverse Event (SAE)

An adverse reaction is ‘serious’ if it:

- Results in death;
- Is life-threatening;
- Requires hospitalisation or prolongation of existing hospitalisation, excluding hospitalisation for planned therapy or convenience of the participant;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect;
- Is a medically important event.

Unexpected Adverse Reactions

An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about the medicinal product in question set out:

- In the case of a product with a marketing authorisation, in the summary of product characteristics for that product;
- In the case of any other investigational medicinal product, in the IB relating to the trial in question.

8.3.2 Reporting of Adverse Events

All adverse events must be fully recorded in the patient's eCRF from signing of informed consent until 30 days after the last dose of Cantrixil, whether or not they are considered to be drug-related. Adverse events that occur within the second and third month of the follow-up period should only be recorded if the investigator deems them to be related to the investigational agent. Signs and symptoms of each AE should be described in detail: onset time and date, offset time and date, description of event, severity, relationship to investigational product, action taken and outcome. The descriptions and grading scales found in the revised NCI-CTCAE version 4.03 will be utilised for AE reporting.

Adverse events should be followed until recovery to the normal state has been achieved. In the event of a patient not returning to the study centre, the outcome of this event will be recorded as lost at follow-up.

Reporting of SAEs and SUSARs

SAEs occurring from the time of informed consent will be reported to the Sponsor's medical representative within 24 hours of the Investigator becoming aware of the event. The Investigator will be requested to complete a separate SAE reporting form in addition to the information in the eCRF.

A suspected unexpected serious adverse reaction (SUSAR) which is fatal or life-threatening must be reported to the competent authority and Ethics Committee immediately (within 7 days or according to local reporting requirements)) after the Sponsor became aware of the event. Any additional information must be reported within eight days of sending the first report.

A SUSAR which is not fatal or life-threatening must be reported to the competent authority and Ethics Committee as soon as possible (within 15 days or according to local reporting requirements) after the Sponsor becomes aware of the event.

8.3.3 Categorisation of Adverse Events

Adverse events will be graded according to the NCI-CTCAE version 4.03. Events which do not fit into any CTCAE category will be categorised as follows:

1	Mild:	Mild events are those which are easily tolerated with no disruption of normal daily activity.
2	Moderate:	Moderate events are those which cause sufficient discomfort to interfere with daily activity.
3	Severe:	Severe events are those which incapacitate and prevent usual activity.
4	Life-threatening:	Life-threatening events have extremely serious consequences and urgent intervention is indicated to avoid a fatal outcome.
5	Death:	Death related to an AE

8.3.4 Causal Relationship Assessment

The Principal Investigator will assess causal relationship between the study treatment and each AE, and answer '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?'. For SAEs causal relationship will also be assessed for study treatment, other medication and study procedures.

8.3.5 Action Taken

Action taken will be defined as:

- None;
- Dosing interrupted;
- Dosing stopped;
- Infusion delay.

8.3.6 Outcome

Outcome will be defined as:

- Not recovered/not resolved;
- Recovered/resolved;
- Recovered/resolved with sequelae;
- Fatal;
- Unknown/lost to follow-up.

8.3.7 Coding of Adverse Events

All AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be categorised for severity according to the NCI-CTCAE Version 4.03.

8.3.8 Pregnancy Reporting

All pregnancies should be reported by the Investigator within 24 hours of notification on a Pregnancy Report Form.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented accordingly on the Pregnancy Report Form.

Although pregnancy itself is not regarded as an AE, congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

8.4 Clinical Laboratory Safety Tests

Sample collection times are included in the Schedule of Assessments (see Section 16).

Clinical laboratory tests include haematology, serum chemistry and urinalysis and are listed below.

Panel	Parameter	
Haematology	White blood cell count	Neutrophils absolute
	Red blood cell count	Lymphocyctes absolute
	Haemoglobin	Monocytes absolute
	Haematocrit	Eosinophils absolute
	Mean corpuscular volume	Basophils absolute
	Mean corpuscular haemoglobin	Platelets
	Mean corpuscular haemoglobin concentration	
Serum biochemistry	Alkaline phosphatase	Sodium
	Alanine aminotransferase	Potassium
	Creatine kinase	Urea
	Gamma glutamyl transpeptidase	Creatinine
	Lactate dehydrogenase	Albumin
	Aspartate aminotransferase	Calcium
	Total Bilirubin	Phosphate
	Globulin	Glucose
	Chloride	Magnesium
Coagulation	Activated partial thromboplastin time	International normalised ratio
Urinalysis (Dip-stick)	Leucocytes	Red blood cells
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy (if clinically indicated)	
Pregnancy test (serum)	Beta human chorionic gonadotropin	

Additional and repeat testing may be performed at the discretion of the Investigator.

Unless otherwise specified in the Laboratory Manual all clinical laboratory tests will be performed by an accredited local laboratory near or at the study centre.

8.5 Clinical Safety Assessments

Assessment times are included in the Schedule of Assessments (see Section 16).

8.5.1 Physical Examination

Physical examinations will be performed by a physician and will include the examination of the following: general appearance, head, eyes, ears, nose, throat, chest/ respiratory, heart/ cardiovascular, gastrointestinal/ liver, musculoskeletal/ extremities, dermatological/ skin, thyroid/ neck, lymph nodes, neurological/ psychiatric. Complete physical examinations will be performed at screening and the final study visit. Symptom-driven physical examinations will be performed where indicated at other specified time points, per the Schedule of Assessments (Table 4).

8.5.2 Vital Signs

Systolic and diastolic blood pressure (SBP, DBP), pulse rate, respiratory rate and body temperature will be recorded as specified in the Schedule of Assessments (Table 4) after the subject has been in a supine position for at least 5 minutes. Blood pressure, pulse rate, and respiratory rate should be obtained at a comfortable room temperature, with the subject's arm unconstrained by clothing or other material. All measurements will be obtained from the same arm and, using an automatic instrument with a digital readout, throughout the study. All readings must be recorded in the eCRF. Additional readings may be taken at the discretion of the Investigator.

8.5.3 12-Lead Electrocardiogram (ECG)

Computerised 12-lead ECG recordings will be obtained according to the Schedule of Assessments (Table 4). Each lead shall be recorded for at least 3 beats at a paper speed of 25 mm/sec. Subjects will rest in a supine position for at least 5 minutes prior to recordings. Recordings will be obtained in triplicate.

The following parameters will be recorded: rhythm, ventricular rate, PR interval, QRS duration and QT. The RR value will also be recorded so that the QTcF values can be calculated automatically by formula.

Where the ECG is recorded as abnormal, the abnormality will be specified.

8.5.4 Medical History

A complete medical history will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose throat, chest/ respiratory, heart/ cardiovascular, gastrointestinal/ liver, gynaecological/ urogenital, musculoskeletal/ extremities, skin,

neurological/ psychiatric, endocrine/ metabolic, hematologic/ lymphatic, allergies/ drug sensitivities, past surgeries and clinical outcomes, substance abuse or any other diseases or disorders. All prior cancer treatments and the clinical outcomes will also be recorded.

8.6 Follow-up Assessments

Patients will be followed for 3 months after discontinuing therapy or until death or consent withdrawal, whichever occurs first (see Schedule of Assessments in Follow-up, Table 6). Patients withdrawing consent for the study, who have study-related AEs, are encouraged to continue visits until resolution or stabilisation of the AEs. Patients that are beginning on another treatment therapy before the end of the follow-up period must be formally withdrawn from this study. In this case, safety data should be collected until the day before the first study intervention on the new study.

9 DATA COLLECTION

A 21 CFR part 11 compliant Electronic Data Capture (EDC) system will be used for this study. Electronic CRFs will be utilised. An eCRF is required to be completed for each subject who provides informed consent. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. Any corrections to entries made in the source documents must be dated, initialled and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the study centre or the physician's subject chart or patient medical record. In these cases, data collected on the eCRFs must match the data in those charts or medical records. All source documents will be retained by the study centre.

In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the study centre as well as at the Sponsor clearly identifying those data that will be recorded in the eCRF, and for which the eCRF will stand as the source document

Photocopies of completed source documents will be provided only if essential (i.e. for regulatory purposes) at the request of the Sponsor.

The informed consent will be kept at the study centre with a copy of the completed source documents in the appropriate Investigator site file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the course of the study. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct. 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. Final data will be extracted from the EDC and delivered to the Sponsor in the form of SAS® datasets. A PDF copy of the eCRF will be produced for each study subject and included in the final delivery.

All eCRF entries, corrections, and alterations must be made by the Investigator or other, authorised, study centre personnel and only by individuals who have received training on the EDC system. Study centre personnel may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

Adverse events will be coded using the current MedDRA thesaurus; concomitant medication will be coded using the World Health Organisation (WHO) Drug Dictionary (DD) (if required).

The EDC system will keep track of all data entries, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside the data.

10 EVALUATION OF STUDY DATA

10.1 Evaluation of Pharmacokinetic Parameters

Summary statistics will be presented for Cantrixil (TRX-E-002-1) plasma concentrations at each scheduled time point by dose cohort (for example, mean, geometric mean, median, standard deviation [SD], standard error of the mean [SEM], coefficient of variation [CV] and range). Summary statistics will also be presented by dose cohort for all Cantrixil PK parameters, including

- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$),
- Maximum plasma concentration (C_{max}) and
- Time to maximum plasma concentration (t_{max}), plus if estimable:
- Area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$),
- Apparent terminal half-life ($t_{1/2}$),
- Clearance (CL) and
- Volume of distribution (Vd).

All concentrations below the limit of quantification and/or missing data will be labelled as such in the concentration data listings. Concentrations below the limit of quantification which are after C_{max} will be treated as missing in summary statistics and for the calculation of pharmacokinetic parameters. Pharmacokinetic parameters will be determined by standard non-compartmental pharmacokinetic analyses using Phoenix 64 WinNonLin software.

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

10.2 Evaluation of Pharmacodynamic/Efficacy Measures

Not applicable.

10.3 Evaluation of Safety

The safety evaluation will include vital signs, ECG parameters, clinical laboratory tests (haematology, serum biochemistry, coagulation, urinalysis and urine microscopy [if clinically indicated]) and AEs.

11 STATISTICAL METHODS

The default summary statistics for continuous variables include number of contributing observations (n), mean, SD, median, minimum and maximum.

For categorical variables, the number (n) and percentage (%) (the percentage of subjects in each category relative to the total number of subjects in the relevant analysis population or relative to the total number of subjects in the relevant analysis population, with assessments available [where appropriate]) in each category will be the default summary presentation.

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.

Unless otherwise specified, all statistical estimates will be provided at the 5% significance level. In case of normality assumption violation, an appropriate non-parametric method will be used for analysis, where applicable.

All data will be presented in by-subject listings.

The statistical analysis will be performed using SAS® Version 9.2 or higher.

All details regarding the statistical analysis 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.

11.1 Sample Size Determination

For this Phase I dose-escalation study to determine the MTD of Cantrixil as a monotherapy and to investigate the safety and tolerability as combined with standard chemotherapy, an appropriate sample size is not statistically determined.

The dose-escalation Cycle 1/Part A of the study is designed to determine the MTD of Cantrixil as a monotherapy in patients with ovarian cancer, Fallopian tube cancer or primary peritoneal cancer. The planned dose levels include 0.24, 0.6, 1.25, 2.5, 5, 10 and, 20 mg/kg. From initial dose level, single patient cohorts will be used until an AE is observed during Part A/Cycle 1 that meets the definition of a DLT or warrants further examination in the opinion of the Principal Investigator and the DSMC/B (see Section 6.1) and then the dose escalation will follow the 3+3 dose escalation model to treat up to 3 to 6 patients at each escalating dose level. After Cycle 2, which is another cycle of Cantrixil monotherapy, patients will continue at the same dose level combined with standard chemotherapy through Cycles 3 to 8 in Part A of the study. Patients who don't experience a DLT but who do not complete Cycle 1 of therapy will be replaced. To

establish MTD in Part A/Cycle 1 of the study, up to 42 patients will be enrolled. An expanded cohort with 12 patients will be enrolled and treated at MTD in Part B of the study.

The total sample size may be up to 54 patients (up to 42 in Part A, 12 in Part B) enrolled into this study.

11.2 Subject Populations for Analyses

Maximum Tolerated Dose (MTD) population:

The MTD population will include all patients who experienced DLTs in Cycle 1/Part A, and those who received all three weekly doses of study treatment in Cycle 1/Part A. The safety data regarding the Cycle 1/Part A will be used to determine MTD from this analysis population.

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.

Pharmacokinetic (PK) population:

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

Intent-to-Treat (ITT) population:

The ITT 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.

The number and percentage of the patients included in the analysis populations will be reported in a table showing the reason of exclusion for all patients enrolled into study. A listing of reasons of exclusion from analysis population will be provided. Patients who were screened but never started a dose will be listed. Screening failures will not be included in any of the summary tables.

11.3 Pharmacokinetic Analysis

Summary statistics will also be presented by dose cohort for all Cantrixil PK parameters described in Section 10.1.

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

11.4 Efficacy Analysis

Disease response will be measured using RECIST version 1.1 criteria; disease response may also be assessed using the Gynecological Cancer Intergroup (GCIG) response criteria that incorporates CA-125 measurements during Follow-up (see Appendix C). Assessment of target lesions response (Complete Response; Partial Response; Progressive Disease; Stable Disease), non-target lesions response (Complete Response; Stable Disease; Partial Response) and CA-125 expression changes will be summarised using frequency and percentage of patients in each response category by dose cohort. Responses will be reported separately for both RECIST 1.1 and CA-125 criteria.

The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for PFS.

The time to paracentesis data will also be summarised as another time-to-event endpoint.

The volume of abdominal fluid will be summarised using descriptive statistics by dose cohort.

11.5 Exploratory Analysis

Enumeration and Clonogenicity of CETC in peripheral blood and malignant ascites will be performed at baseline, at the end of Cycle 2 and at the End of Therapy. Continuous response data (CETC numeration) will be summarised for each dose cohort. For continuous data like CETCs, number of colonies and number of colonies positive per mL of blood and/or per CETC for a stem cell marker, descriptive statistics will be provided.

More details on analysis method or data presentation will be described in the SAP.

11.6 Safety Data Analysis

Demographic and baseline disease characteristics data including age, gender, height, weight, tumour type, medical condition, etc. will be listed individually by patient and summarised descriptively by dose cohort using descriptive statistics (number of observations, median, minimum, maximum, mean and SD). Categorical variables (gender, ethnicity and race) will be summarised using frequencies and percentage. The SAF population will be used.

Maximum tolerated dose

For determination of the MTD, individual subject 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 subjects in the DLT population who experience a DLT during the first DLT evaluation period (Cycle 1/Part A).

- At each dose level, the number and proportion of treatment emergent AEs (TEAEs) experienced by subjects in the DLT population during the first DLT evaluation period (Cycle 1/Part A).

The MTD will be determined according to the dose-escalation plan described in Section 6.1.2 (Table 3).

The MTD is defined as the highest dose level at which no more than 1 subject out of 6 subjects treated in a cohort and evaluable for DLT determination experiences a DLT.

Safety and tolerability

Safety analyses will be performed on the SAF population.

Adverse events will be coded using MedDRA and will be summarised by System Organ Class (SOC), Preferred Term, and dose cohort. Severity of AEs will be graded using the CTCAE version 4.03 toxicity grading scale. Adverse events will be further summarised by maximum severity and relationship to study treatment. Prior and concomitant medications will be summarised by dose cohort. Standard chemotherapy medications will be separately summarised by dose cohort. Safety laboratory tests and vital signs assessments, will be summarised by dose cohort using statistics for continuous or categorical data, as appropriate.

Dose limiting toxicities, safety and tolerability data will also be separately summarised for Cycles 1 and 2, and Cycles 3 to 8 at MTD from Part A and Part B study, as appropriate. A detailed SAP will be finalised prior to clinical database lock of the study.

Concomitant Medications

All medications will be coded using the WHO-DD and Anatomical Therapeutic Chemical (ATC) system. Each medication will be classified as prior medication if it is stopped prior to the first dose of Cantrixil, or as concomitant medication if it is on-going at the time of the first dose or is started after the first dose of Cantrixil. Prior and concomitant medications will be summarised by dose cohort by ATC level 2 categories and preferred name.

Standard chemotherapy medications and regimen of patients will be summarised and listed separately.

Laboratory abnormalities

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges. For each laboratory test (e.g. haematology, biochemistry) a listing of laboratory values will be provided by laboratory parameter, patient and dose cohort. The frequency of

notable lab abnormalities (i.e. newly occurring CTCAE Grade 3 or Grade 4 laboratory toxicities), will be displayed by parameter, cycle, and dose cohort. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE Grade 3 or Grade 4 laboratory toxicities).

Laboratory data will be summarised by presenting grade shift tables for those parameters for which CTCAE version 4.03 allows classification. All remaining data will be summarised by presenting shift tables based on normal ranges. Laboratory data will also be displayed by presenting descriptive statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

Vital Signs

Vital signs results will be presented using descriptive statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

Physical Examinations

Physical examination results will be summarised using frequency tables for normal/abnormal results per visits.

12 STUDY REPORT

A clinical study report, compliant with the requirements of ICH E3, will be prepared by IQVIA.

13 REGULATORY AND ETHICAL ISSUES

13.1 Regulatory and Ethics Review and Approval

This study is to be conducted according to globally accepted standards of GCP (as defined in the ICH E6 Guideline for GCP), in agreement with the latest revision of the Declaration of Helsinki and in keeping with local regulations. Before initiation of the study, approvals from the applicable Regulatory Authority(ies) will be obtained where relevant. The Investigator must obtain approval or favourable opinion of the protocol, Informed Consent Form (ICF) and any advertisement for patient recruitment from the Ethics Committee complying with the applicable pertinent government regulations. The Ethics Committee will evaluate the ethical, scientific and medical appropriateness of the study.

The documents submitted will include but are not limited to;

- The final protocol,
- The IB,
- The ethics application form,
- The ICF.

The study will not commence unless the following conditions are satisfied:

- The IRB has given a favourable opinion in relation to the study; and
- The study has been authorised by the licensing authority.

13.2 Informed Consent

Before any study-related activities are carried out such as Screening and enrolment, each prospective candidate will be given a full explanation of the study, allowed to read the approved ICF in a local language and will be provided ample time and opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the individual understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing and personally dating the ICF. The Investigator will provide a copy of the signed and dated ICF to each patient.

The nature of the ICF will comply with the current version of the Declaration of Helsinki, the current requirements of GCP and local regulations, which ever provides the greater patient protection.

If an amendment to the Clinical Study Protocol (CSP) changes the patient participation schedule in scope or activity, or increases the potential risk to the patient, the ICF must be

revised and submitted to IRB for review and approval or favourable opinion. The revised ICF must be used to obtain consent from any patient currently enrolled in the study if he/she is affected by the amendment. The revised ICF must be used to obtain consent from any new patients who are enrolled into the study after the date of the approval or favourable opinion of the amendment by IRB.

The signed and dated declaration of informed consent will remain at the Investigator's study centre, and must be safely archived by the Investigator so that the ICFs can be retrieved at any time for monitoring, auditing, and inspection purposes.

13.3 Indemnity and Compensation

The Sponsor will indemnify the Investigators from all and any claims arising out of this study except for their negligence or malpractice and providing that the study is conducted according to the standards established by the protocol.

In the event that it can be demonstrated that a patient suffers any significant deterioration in health or well-being or any harmful susceptibility or toxicity as a direct result of their participation in this study then the Sponsor will agree to abide by the current Food and Drug Administration Guidelines, as well as any local regulations that may apply, with regard to compensation payable to the patient. The amount of compensation will be calculated by reference to the level of damages commonly awarded in law for similar injuries at the time when such an injury occurred.

The Investigators declare to having insurance cover for the malpractice and/or negligence of their employees and agents.

14 STUDY MANAGEMENT

14.1 Quality Assurance and Quality Control

In accordance with the guideline for ICH GCP, the Sponsor has responsibility for implementing and maintaining quality assurance and quality control systems, and the ultimate responsibility for the quality integrity of the trial data resides with the Sponsor.

Data will be captured in a standardised format according to the study centre's standard operating procedures and those procedures specified in the study documentation.

A 21 CFR part 11-compliant EDC system will be used for this study. The eCRFs will be produced for each patient.

The Investigator will ensure the accuracy, completeness and timeliness of the data recorded for data queries and all required reports according to any instructions provided.

14.2 Protocol Adherence

The protocol must be read thoroughly and the instructions followed exactly. Any deviations should be agreed by both the Sponsor and the Investigator, with the appropriate written and approved protocol amendments made to reflect the changes agreed upon. Where the deviation occurs for the well-being of the patient, the Sponsor must be informed of the action agreed upon. No prospective protocol waivers will be granted by the Sponsor.

14.3 Documents Necessary for Initiation of Study

The following documents will be available prior to the first administration of the study treatment to the first patient:

- Regulatory authorisation;
- Copy of current Investigator's Brochure;
- Risk assessment report;
- Completed and signed Investigator agreement/contract;
- Signed original of the final protocol;
- Ethics Committee approval;
- Copy of the constitution of the Research Ethics Committee;
- A list of members of the Ethics Committee;
- A copy of the consent form and patient information to be used;
- The curriculum vitae of all Investigators;

- A clinical trial agreement between the Sponsor and the study centre defining the responsibilities of the Sponsor, the study centre and any third parties significantly involved in the supply chain of the IMP, where applicable;
- A list of laboratory reference range values for parameters measured in the study.

14.4 Study Monitoring

The study will be monitored in accordance with ICH GCP guidelines. The clinical monitor, whether an employee of the Sponsor or its designated representative, has the obligation to closely follow the study. In order to fulfil this obligation, the study monitor will visit the study centre at periodic intervals, in addition to maintaining necessary telephonic and correspondence contact. The clinical monitor will observe current personnel knowledge of the study through observation, review of the study records and source documentation, as well as discussions with the Investigator and study centre staff. Quality assurance auditors, whether employees of the Sponsor or its designated representative, may also evaluate the conduct of the study at the study centre at any time during or after the study to ensure the validity and integrity of the study data. These parties must have access to all study reports and source documentation, regardless of location and format.

Upon completion of the study, the clinical monitor will arrange for a final review of the study files, after which the files should be secured for the appropriate time. The Investigator, or appointed delegate, will meet with the monitor during the study centre visits and co-operate fully in providing the necessary documents for inspection and responding to any queries. In addition, the Investigator will permit inspection of study files by authorised representatives of the Sponsor or regulatory agencies. The Investigator will also allow study-related monitoring audits, Ethics Committee review, and regulatory inspection allowing direct access to the source data/documents.

14.5 Study Closure

The Investigator reserves the right to terminate the study in the interest of subject welfare.

The Sponsor may terminate the study at any time.

Premature termination of the study by any party will be governed under the terms of the contract between the parties and the prevailing safety and well-being of patients.

14.6 Study Record Retention

In accordance with SI 1928, the Sponsor and the Principal Investigator shall ensure that the documents contained, or which have been contained, in the Trial Master File are retained for at least 15 years after the conclusion of the study and that during that period are:

- Readily available to the licensing authority on request; and
- Complete and legible.

All data derived from the study will remain the property of Kazia Therapeutics Limited. The study will be the subject of a final CSR compiled by, or by order of Kazia Therapeutics Limited in consultation with the Principal Investigator following the guidance in ICH Topic E3.

All correspondence (e.g. with the Sponsor, Ethics Committee) relating to this study should be kept in the appropriate file folders.

Records of patients' source documents, eCRF's, IMP inventory, pertaining to the study must be kept on file. Records must be retained according to the current ICH Guidelines on GCP.

The records should be retained by the investigator according to the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, local regulations, or as specified in the Clinical Study Agreement, whichever dictates a longer period. The Sponsor shall appoint named individuals within their organisation to be responsible for archiving the documents which are, or have been, contained in the Trial Master File. Access to those documents shall be restricted to those appointed individuals. If there is transfer of ownership of data or documents connected with the clinical study:

- The Sponsor shall record the transfer; and
- The new owner shall be responsible for data retention and archiving.

If the Investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

14.7 Publication Policy

After completion of the study, the Investigator may prepare a joint publication with the Sponsor. The Investigator must undertake not to submit any part of the individual data from this protocol for publication without prior consent of the Sponsor at a mutually agreed time.

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16 STUDY SCHEDULE

The procedures and assessments to be performed during each part of the study are outlined in the Schedule of Assessment (Table 4), the Schedule of PK Assessments (Table 5) and the Schedule and Assessments in Follow-up (Table 6).

Actual Cantrixil and chemotherapy administrations and the date and time of study assessments will be recorded in the patient's eCRF. If any abnormalities in safety assessments are observed, repeat measurements may be performed at the discretion of the Investigator.

Table 4 Schedule of Assessments

	Screening[#]	Part A and B: Cycle 1			Part A and B: Cycles 2 to 8			Continued Access	[d]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]			
	Part A Screening[#]	Part A: Cycle 1			Part A: Cycles 2 to 8				
Biomarker Samples – Part A only	X[e]				X[e]				X[e]

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 1 of Cycle 3 before IP administration) and End of Therapy, during Part A of the study only.

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.

Safety Panel	**Test Parameter**	
Haematology	White blood cell count	Neutrophils absolute
	Red blood cell count	Lymphocyctes absolute
	Haemoglobin	Monocytes absolute
	Haematocrit	Eosinophils absolute
	Mean corpuscular volume	Basophils absolute
	Mean corpuscular haemoglobin	Platelets
	Mean corpuscular haemoglobin concentration	
Serum biochemistry	Alkaline phosphatase	Sodium
	Alanine aminotransferase	Potassium
	Creatine kinase	Urea
	Gamma glutamyl transpeptidase	Creatinine
	Lactate dehydrogenase	Albumin
	Aspartate aminotransferase	Calcium
	Total Bilirubin	Phosphate
	Globulin	Glucose
	Chloride	Magnesium
Coagulation	Activated partial thromboplastin time	International normalised ratio

Table 5 Proposed PK Schedule (Part A and Part B)

PK Time Point	Cycle:Day:Hour:Minute[a]	Rationale
T1	Cycle 1 D1 00:00 (pre-dose)	Baseline before Cycle 1
T2	Cycle 1 D1 00:05 (end of infusion)	Samples to measure t_{max} and $t_{1/2}$ after first monotherapy dose/ first exposure
T3	Cycle 1 D1 00:30 post-dose	
T4	Cycle 1 D1 01:00	
T5	Cycle 1 D1 02:00	
T6	Cycle 1 D1 04:00	
T7	Cycle 1 D1 06:00	
T8	Cycle 1 D2 24:00	
Process, freeze and batch above samples; ship for analysis on D3 of Cycle 1 (or following Monday to avoid weekend arrival at TetraQ)		
T9	Cycle 3 D1 00:00 (pre-dose)	Check no accumulation after Cycles 1 and 2
T10	Cycle 3 D1 00:05 (end of infusion)	To facilitate the interpretation of any differences seen between Cycle 1/D1 and Cycle 3/D8. Without data from Cycle 3/D1, we won't be able to conclude whether differences between Cycle 1/D1 and Cycle 3/D8 are attributable to repeated dosing with Cantrixil or an interaction with the combination chemotherapy.
T11	Cycle 3 D1 00:30	
T12	Cycle 3 D1 01:00	
T13	Cycle 3 D1 02:00	
T14	Cycle 3 D1 04:00	
T15	Cycle 3 D1 06:00	
T16	Cycle 3 D2 24:00+ (before combination chemotherapy administration)	Check efficient elimination of Cantrixil before administration of combination chemotherapy to avoid any drug-drug interactions.
T17	Cycle 3 D8 00:00 (pre-dose)	Baseline Before Combination Chemotherapy Dose
T18	Cycle 3 D8 00:05 (end of infusion)	Samples to measure t_{max} and $t_{1/2}$ after first combination therapy dose/ check whether combination therapies alter PK
T19	Cycle 3 D8 00:30	
T20	Cycle 3 D8 01:00	
T21	Cycle 3 D8 02:00	
T22	Cycle 3 D8 04:00	
T23	Cycle 3 D8 06:00	
T24	Cycle 3 D9 24:00	
Process, freeze and batch above samples; ship for analysis on D10 of Cycle 3 (or following Monday to avoid weekend arrival at TetraQ)		

PK: Pharmacokinetics

a A 15-minute window will be allowed for samples taken pre-dose; a 5-minute window will be allowed for samples taken up to and including 1-hour post-dose; a 15-minute window for samples taken 2 to 6 hours' post-dose and a 2-hour window for samples taken 24 hours' post-dose.

Table 6 Schedule of Assessments in Follow-up

	4* weeks follow-up	8* weeks follow-up	12* weeks follow-up
Concurrent meds	X	X	X
Physical exam	X	X	X
Vital signs	X	X	X
Weight	X	X	X
Performance Status	X	X	X
Safety Laboratory Assessments	X	X	X
CA-125 testing	X	X	X
ECG (if indicated)			
AE evaluation	X		
Radiologic evaluation[b]		X[b]	X
Tumour measurements		X	X

* ±1 week is acceptable

AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood Urea Nitrogen; CBC: complete blood count; CT: Computed Tomography; ECG: electrocardiogram; LDH: Lactate dehydrogenase; LFT: liver function test; MRI: Magnetic Resonance Imaging, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvate transaminase

a CBC with differentials and platelets, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium. Include serum urea nitrogen; serum creatinine.

b The Principal Investigator can use the imaging modality of preference (either MRI or CT) but the same modality must be used for all time-points; the tumour measurement can be done between 6 and 8 weeks.

17 PROTOCOL SIGNATURES

INVESTIGATOR SIGNATURE:

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

Principal Investigator <Insert name and qualifications> <Insert name of institution>	Date

SPONSOR SIGNATURE:

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Investigator has the right to discontinue the study at any time. I have read the protocol and understand it and will ensure that the clinical trial is conducted according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

Sponsor's Representative Dr James Garner Chief Executive Officer Kazia Therapeutics Limited	Date

APPENDIX A: STUDY CONTACTS

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APPENDIX B: PROCEDURES FOR THE PLACEMENT OF THE INTRAPERITONEAL PORT/ CATHETER AND ADMINISTRATION OF INTRAPERITONEAL THERAPY

This appendix is included as a guideline to aid investigators and does not have to be followed explicitly. Each site should rather follow their own standard operating procedures for the placement of ports or catheters for intraperitoneal chemotherapy and intraperitoneal chemotherapy administration.

The following device specifications have been adapted from recommendations of the Gynaecological Oncology Group recommendations for intraperitoneal chemotherapy: "Silicone catheters are preferred. Controversy exists between the use of venous 9.6 silicone catheters or silicone intraperitoneal ports with fenestrations. Bardport silicone peritoneal catheter 14.3 Fr (Reorder number 0603006) that is without a cuff, is the preferred intraperitoneal catheter. This has been FDA approved for use in intraperitoneal therapy. The 9.6 Fr single lumen intravenous access device, if made with silicone is preferred by many surgeons. Brand names are different for different institutions due to contracting, and these specifications are intended to be helpful but not limiting. Equivalent or similar devices are acceptable if made from silicone, large enough not to kink, and without a Dacron cuff. Examples of these include: Bardport MRI Implanted Port reorder number 0602680 attachable 9.6 Fr open ended single lumen silicone venous catheter. Titanium Dome Implanted Port with attachable 9.6 Fr open ended Single lumen venous catheter. Reorder number 0602870. Bard Access Systems 5425 West Amelia Earhart Drive Salt Lake City Utah 84116 1-800 545-0890.

Procedure at the time of a planned laparotomy:

1. At the completion of the laparotomy just prior to closing the incision, make a 3 to 4cm incision over the lower costal margin on the side where the catheter is to be placed. The incision is carried down to the fascia using blunt and sharp dissection.
2. A subcutaneous pocket superior to the incision is fashioned slightly larger than the diameter of the portal.
3. Select an area several centimetres below and lateral to the umbilicus as the peritoneal entrance site of the catheter. Prepare a subcutaneous tunnel from the portal pocket to the site in the peritoneal cavity. You want the catheter to enter the abdomen; draw the catheter through the subcutaneous tissue into the abdomen using a tunnelling device.
4. Attach the catheter to the portal as per manufacturer's instructions, and suture the portal in place with permanent suture (i.e., 2-0 prolene) to the fascia overlying the

rib cage. Be sure the chemotherapy nurses will be able to feel the port and stabilise it on the chest wall for easy access with Huber needle in the future. Be sure the Huber needle will not have to go through the wound to access the port; the port should lie superior to the port incision site.

5. After flushing the system with heparin, 100 units per mL, to determine that flow is not obstructed and no leaks exist, place the distal end of the catheter to the desired infusion site, with at least 10 cm of free catheter in the abdomen. Do not allow the catheter to be long enough to reach the bladder, vagina or rectum.
6. Close incisions and place a Huber needle trans-dermally into the portal if the catheter is going to be irrigated in the immediate postoperative period. Wait a minimum of 24 hours prior to treating patient after intraperitoneal port placement, and wait for return of gastrointestinal function (regular diet tolerated and normal bowel movement) after major laparotomy.

Surgical implantation with mini lap. (Video available at SGO.org and GOG.org):

1. Select a site several centimetres below and lateral to the umbilicus and make an incision through skin, subcutaneous tissue and fascia. Separate rectus muscle and enter peritoneum. Knowledge of the previous surgical resections and current anatomy will assist in choosing location.
2. Pull the catheter from subcutaneous tissue into the peritoneal cavity through the full thickness of the abdominal wall (fascia, muscle, peritoneum) from an adjacent location (not through the incision) while under direct visualisation to prevent injury to bowel. This can be accomplished with a tonsil clamp or tunnelling device.
3. The catheter must be left in the abdominal cavity at least 10 cm to prevent migration out of the peritoneal cavity.
4. The opposite end of the catheter is tunnelled up to the costal margin where it is attached to an implanted port as described above. The catheter is left long enough to not retract, but not long enough to reach vagina, rectum or bladder. It is generally left at least 10 cm into the peritoneal cavity.

Surgical implantation using laparoscopy:

1. Laparoscopic placement of an intraperitoneal catheter is usually feasible from a left upper quadrant approach. Knowledge of the previous procedures performed (i.e. bowel resections and re-anastomosis sites) and location of the tumour will inform the surgeon as to the best approach and what locations to avoid.

2. Once the peritoneal cavity can be visualised, a second puncture can be used to gain access to the peritoneal cavity for the catheter, and then the catheter tunnelled in the subcutaneous tissues to the planned port pocket.

Interventional radiology can place intraperitoneal ports in some institutions. This requires a great communication between the treating oncologist and the radiologist to get the best result. Knowledge of the anatomy and best sites for peritoneal access should be communicated. CT or ultrasound directed access to the peritoneal cavity can allow catheter placement and then subcutaneous tunnelling to the lower chest wall for appropriate port placement and catheter attachment.

Administration of intraperitoneal therapy:

Treatment may be administered on an outpatient basis if deemed appropriate by the Investigator. To allow for PK sampling, the infusion on Day 1 of Cycle 1 should begin early in the day. Scheduling Day 1 to occur on a Monday is ideal, particularly for the later cycles, so that dosing visits are always on weekdays.

Cantrixil must be delivered only via the intraperitoneal route. Cantrixil will be ordered, stored, prepared and handled as described in Section 7.1.2. It will be delivered as a saline infusion at a dose allocated to the patient upon enrolment. The timing of the preparation of Cantrixil is critical. Both Cantrixil and any subsequent distributional infusion must be at body temperature before administration. Pharmacy should be notified when the patient is present in the infusion suite so that they can prepare any appropriate pre-medications. The choice and administration of any pre-medications, including anti-emetics and analgesia, should follow local standard operating procedures for intraperitoneal chemotherapy. Cantrixil is a CYP450 inhibitor; this must be kept in mind when selecting concomitant medications.

Whilst the pre-medications are being administered, the pharmacy can prepare the 100 mL Cantrixil infusion and the extra 1 L saline infusion and warm the solutions according to institutional practice, for example using a warm water bath or blood warmer.

For accession, the patient should be placed supine in semi-Fowler's position on a stretcher, adjustable bed or Gurney. Emla 2.5% cream may be applied to the port site and covered with occlusive dressing one hour before accessing the port. The reservoir should be accessed under sterile technique, generally using a right-angle, non-coring, 20 gauge, 1.25-inch gripper-type Huber needle and flushed. A longer needle may be necessary for patients with thick subcutaneous tissue on the chest wall. The port should flush easily without pain or oedema at the site. Difficult or uncertain accessions can be verified by anterior-posterior and lateral radiographs. The needle can then be secured using a temporary adhesive dressing. The head of the bed should be raised no higher than 30 degrees to prevent dislodgement of the needle during infusion. A flat position during infusion may cause increased pressure on the diaphragm causing respiratory

compromise/GI discomfort in patients receiving intraperitoneal infusions. The 100 mL Cantrixil solution should be infused first under gravity. Infusion pumps are not recommended because they can cause needle dislocation (Hoskins, 2006). Then, to facilitate distribution, up to 1 L of warmed normal saline is infused to patient tolerance.

The position of the needle in the reservoir should be carefully determined and recorded at 15-minute intervals. Ambulation is restricted as much as possible during infusion to avoid dislodgment of the needle. Patients should be encouraged to use the toilet before the procedure begins. If the bedpan is required, then the nurse or Investigator should check the proper needle position is maintained (GOG).

The infusion nurse or physician should be aware of and check for the following complications which may arise during administration: nausea, vomiting, diarrhoea, gastro-oesophageal reflux, pain in the abdomen, chest or port site, excess abdominal distention, tenderness, fever, chills, dyspnoea, changes in mental status, tremors, and weakness. Most patients will experience some degree of abdominal bloating and discomfort during the infusion. The nurse or physician is responsible for determining when that discomfort is appropriate to the process and when it signifies that there may be a problem. In the former case, the physician or nurse should be able to provide reassurance that these sensations are to be expected and will resolve on conclusion of the infusion. In the latter, the physician or nurse should be able to quickly and easily notify the Principal Investigator of the situation.

After the infusion is complete, the infusion nurse or physician should reposition the patient every 15 minutes for 1 hour in the sequence listed below:

- Head up (30°),
- Slight Trendelenburg,
- Right lateral,
- Left lateral.

(GOG; Hoskins, 2006). If possible, the bed can also be alternated between the Trendelenburg and reverse Trendelenburg positions to facilitate distribution of the infusion.

After removing the Huber needle from the intraperitoneal port site, a pressure dressing should be placed over the port site to prevent reflux of the infusion from the port. Patients can remove the pressure dressing 12 to 24 hours after intraperitoneal infusion

References:

Hoskins, 2006
Hoskins, P. Intraperitoneal therapy for British Columbia. BC Cancer Agency Gynecological Tumour Group (2006)

GOG

GOG web-site: GOG Foundation, www.gog.org

SGO

SGO web-site: Society for Gynecologic Oncology, www.sgo.org

APPENDIX C: EVALUATION OF RESPONSE AND PROGRESSION USING GYNECOLOGICAL CANCER INTERGROUP (GCIG) RESPONSE CRITERIA

The Gynecological Cancer Intergroup (GCIG) has published a detailed guidance on the criteria that could be used in clinical trial protocols to define progression and response in recurrent disease using RECIST 1.1 together with the serum marker CA-125 (Rustin et al., 2011). The definitions have been validated and the key summary tables have been reproduced below for guidance.

Definition of a Response

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Patients are only evaluable if they have a baseline measurement that is at least twice the upper limit of normal and with 2 weeks of treatment start. The date when CA-125 levels is first reduced by 50% is the date of the CA-125 response.

To calculate CA-125 responses, the following rules must apply:

1. Intervening samples and the 28-day confirmatory sample must be less than or equal to the previous sample (within an assay variability of 10%).
2. The same validated assay must be used for each patient
3. Patients are not evaluable by CA-125 if there has been a medical and/or surgical interference with their peritoneum during the previous 28 days. For this study, this means that patients are only evaluable for response based on CA-125 levels during the Follow-up period.

CA-125 may be used to evaluate patients without initial measurable disease;

Table 7 summarises the algorithm for determining the best overall response in patients without initial measurable disease and who are evaluable according to 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 Table 8. In patients who have measurable disease by both criteria, the date of response will be the date of the earlier of the 2 events.

Table 7 Evaluation of Best Overall Response in Patients *without* Initial Measurable Disease and who are Evaluable as proposed by GCIG

CA-125	Non-Target Lesions*	New Lesions	Overall Serological Response	Best Response for this Category Also Requires
Response and Normalised	CR	No	CR	Confirmed and maintained for 28 days
Response	Non-PD	No	PR	
Normalised but no Response	Non-CR/Non-PD	No	SD	
Non-PR/Non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD[#]	Yes or No	PD	
Any	Any	Yes	PD	

*Non-target lesions include ascites and peritoneal thickening, which are not measurable by RECIST 1.1
[#]Unequivocal progression in non-target lesions may be accepted as disease progression.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease

Table 8 Best Overall Response in Patients with Measurable Disease and who are Evaluable by CA-125 as proposed by GCIG

Target Lesion*	Non-Target[#]	New Lesion	CA-125	Overall Best Response
CR	CR	No	Normal	CR
CR	Non-CR Non-PD	No	Not PD	PR
CR	CR	No	PR but not normal	PR
CR	NE	No	PR	PR
PR	Non-PD or NAE	No	Not PD	PR
NAE	Non-PD	No	PR	PR
PD or new >28 days from CA-125 PR^			PR	PR
SD**	Non-PD	No	PR	PR
SD**	Non-PD or NAE	No	Not PR and Not PD	SD
PD or new ≤ 28 days from CA-125 PR^			PR	PD
PD	Any	Yes or No	Any	PD
Any	PD	Yes or No	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Yes or No	PD	PD

*Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST1.1
[#]Non-target lesions include ascites and peritoneal thickening, which are not measurable by RECIST 1.1
^Patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA-125 response.
**This protocol specifies that the minimum time between 2 measurements for classification of stable disease is 6 weeks.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease; NAE, not all evaluated; NE, Not evaluated.

Definition of Progression

According to the GCIG progression criteria, patients are not evaluable by CA-125 if there has been a medical/or surgical interference with their peritoneum during the previous 28 days. Hence, during the treatment period of this study, patients will **not** be defined as having progressive disease due to rising CA-125 levels alone. During Follow-up, patients may become evaluable for CA-125 and then the definition in Table 10 below may be used. In assigning the date of progression, PD by objective tumour size should always take precedence over CA-125 should it occur first; although during Follow-up a patient may be declared to have PD on the basis of either the objective RECIST 1.1 criteria or the CA-125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

Table 9 Definition of Progression as proposed by GCIG

GCIG Subcategorised Group	RECIST Measurable/ Non-measurable		CA-125
A = Patients with elevated CA-125 pre-treatment and normalisation of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.	Compared to baseline (or lowest sum while on study if less then baseline), a 20% increase in sum of diameters (RECIST 1.1 definition) OR Any new lesions (measurable or non-measurable) OR Unequivocal increase in non-target disease Date of PD: date of documentation of increase or new lesions	AND/ OR	CA-125 ≥ 2x ULRR documented on 2 occasions* Date of PD: first date of the CA-125 elevation to ≥ 2x ULRR
B = Patients with elevated CA-125 before treatment, which never normalises, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart	As for A		CA-125 ≥ 2x nadir value on 2 occasions* Date of PD: first date of the CA-125 elevation to ≥ 2x nadir value
C = Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.	As for A		As for A

*Repeat CA-125 any time but normally not less than 1 week after the first elevated CA-125 level.
ULRR, upper limit of response range