STUDY PROTOCOL

PiSARRO: p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin/Pegylated Liposomal Doxorubicin Combination Chemotherapy With or Without APR-246

Protocol No.:	APR-407
EudraCT No.:	2013-001472-38
IND No.:	124,841
Coordinating Investigator:	John A Green Department of Molecular and Clinical Cancer Medicine Institute of Translational Medicine University of Liverpool Clatterbridge Centre for Oncology Bebington Merseyside CH63 4JY, UK ***REDACTED***
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PROTOCOL APPROVAL PAGE

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INVESTIGATOR'S STATEMENT

PiSARRO: p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin/ Pegylated Liposomal Doxorubicin Combination Chemotherapy With or Without APR-246.

This page will be institute specific and should list the investigator that will sign-off the separate protocol agreement.

1. I agree to conduct this study as outlined in the protocol.
2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.
3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013).
4. I will enroll patients who meet the protocol criteria for entry.
5. I understand that my signature on each completed Electronic Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Investigator Signature

Name: _____

Title: _____

Signature _____

Date _____

Institution name and address:

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REDACTED

CLINICAL STUDY SYNOPSIS

Name of Sponsor: Aprea Therapeutics AB Nobels väg 3 SE-171 65 Solna Sweden	**Study phase:** Phase Ib/II Study

Name of finished product: APR-246, concentrate for solution for infusion

Name of active ingredient: 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2,2,2]octan-3-one

Title of the study: PiSARRO: p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin/ Pegylated Liposomal Doxorubicin (PLD) Combination Chemotherapy With or Without APR-246.

Investigators and study centers:

Please see Study Operations Manual

Publication (reference): To be confirmed

Clinical phases: Phase Ib/II Study

Study Design:

This study is an open-label, randomized, multi-center Phase II proof-of-concept study with a dose confirmation component (dose confirmation component now completed) to assess whether patients with platinum sensitive recurrent p53 mutated high grade serous ovarian cancer (HGSOC) will benefit from treatment with APR-246 in combination with a carboplatin/pegylated liposomal doxorubicin (PLD) chemotherapy regimen.

All patients will have pre-screening immunohistochemistry (IHC) test that will determine p53 status and therefore the suitability to participate in this study. Patient's archived sections from the original tumor sample will be reviewed by a gynecological pathologist to confirm the diagnosis of HGSOC, and positive staining for p53. Patients without positive p53 staining will not be included.

Patients will be randomly assigned in a 1:1 ratio to receive either:

- Arm A: APR-246 with the carboplatin/PLD chemotherapy regimen,
- Arm B: Carboplatin/PLD chemotherapy alone.

The trial will enroll up to a maximum of 400 patients with positive IHC staining for p53. A CT scan/MRI using RECIST v1.1 criteria will be performed at pre-treatment, after 2 cycles (8 weeks), 4 cycles (16 weeks), and after the last cycle (24 weeks).

At subsequent follow-up visits, tumor assessments by CT scan/MRI will be performed 2 months (± 2 weeks) after the end of treatment visit and every 3 months (± 2 weeks) thereafter, until the documented disease progression, as determined by the Investigator at each site and defined by RECIST v1.1.

Optional frozen/fixed core biopsies will be undertaken after randomization, but prior to any infusion, for all patients and on day 3 in APR-246 patients.

Objectives, Endpoints and Study Treatment:
Objectives:
Primary Objective:

- To assess the efficacy of a combined APR-246 and carboplatin/PLD chemotherapy regimen in patients with platinum sensitive recurrent HGSOC with mutated TP53.

Secondary Objective:

- To assess the safety profile of the combined APR-246 and carboplatin/PLD chemotherapy regimen compared with carboplatin/PLD chemotherapy regimen alone.
- To evaluate potential biomarkers.
- To assess the biological activity in tumor and surrogate tissues.
- To compare quality of life of patients treated with these regimens.

Endpoints:
Primary Endpoint

- Progression-free survival (PFS) based on Blinded Independent Central Review (BICR) is the primary endpoint and is defined as the number of days from the date of randomization to the date of objective disease progression or relapse (according to RECIST v1.1 only) or death due to any cause, whichever occurs first. If neither event occurs, PFS will be censored at the date of the last evaluable tumor assessment. Symptomatic deterioration is not objective disease progression.

Secondary Endpoints

- Best overall response and overall response rate (according to RECIST v1.1 and GCIG criteria)
- Duration of response (complete or partial response)
- PFS by assessment of CA-125 (according to GCIG Criteria)
- Overall survival
- Safety profile based on AEs and laboratory assessments
- Evaluation of biomarkers and tumor activity based on CA-125
- Quality of Life assessment using EORTC Ovarian (QLQ-30 and QLQ-OV28) and the Functional Assessment of Cancer Therapy-Ovarian (FACT-O)

Tumor response data will be summarized at each tumor assessment cycle using the following response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE). Best overall response for a patient is the best response recorded from the start of the treatment until disease progression or death. Best overall response will be summarized as the number (%) of patients in each category of response (CR, PR, SD, PD, and NE). PR and CR must be confirmed by a repeat assessment at least 28 days after the criteria are first met for the response to be considered a PR or CR.

The overall response rate is defined as the percentage of patients with a confirmed response of CR or PR in a given population.

The duration of response (confirmed CR or PR) is defined as the number of days from the date of initial response (not the confirmation date) to the date of objective disease progression or death due to any cause, whichever occurs first. If neither event occurs, duration of response will be censored at the date of the last evaluable tumor assessment. Symptomatic deterioration is not objective disease progression.

Overall survival (OS) is defined as the number of days from the date of randomization to the date of death. In the event of no death, overall survival will be censored at the last known alive date.

Study Treatment:

Arm A (APR-246). Patients will receive a fixed dose of 4.5 g APR-246 (1.5 g of the dose during first 45 minutes followed by 3 g of the dose during 5 hours 15 minutes) on Days 1 to 4, with carboplatin AUC 5 and PLD 30 mg/m^2 administered concurrently on Day 4 (treatment repeated every 28 days for up to six cycles).

Arm B (Control). Carboplatin AUC 5 and PLD 30 mg/m^2 administered on Day 1 of each 28-day cycle, repeated for up to six cycles.

Number of patients:
The trial will enroll up to a maximum of 400 patients with positive IHC staining for p53.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Archived sections from the original FFPE sample reviewed by a gynecological pathologist confirming High Grade Serous Ovarian Cancer, High Grade Serous Peritoneal Cancer or Primary Fallopian Tube Cancer, and positive IHC staining for p53 assessed according to defined standard (as detailed in the laboratory manual). Cases that do not show p53 staining will not be included.
2. Radiologically-confirmed Disease Progression between six and twenty-four (6-24) months after a first or second platinum based regimen.
3. At least a single (RECIST v1.1) measurable lesion.
4. Adequate organ function prior to registration:

a) Bone Marrow Reserve:
- Absolute neutrophil count (ANC) $\geq$ 1.5 x10^9/L,
- Platelets $\geq$ 100 x10^9/L,
- Hemoglobin $\geq$ 9 g/dL.

b) Hepatic:
- Total bilirubin level < 1.5 x ULN,
- ALT and AST < 2.5 x ULN.

c) Renal:
- Calculated creatinine clearance > 30 mL/min.

d) Electrolytes
- Potassium within institutional normal ranges.

5. Toxicities from previous cancer therapies, excluding alopecia, must have recovered to grade 1 (defined by CTCAE version 4.0). Chronic stable grade 2 peripheral neuropathy secondary to neurotoxicity from prior therapies may be considered on a case by case basis by the Principal Investigator.
6. If of childbearing potential, negative pre-treatment serum pregnancy test.
7. If of childbearing potential, willing to use an effective form of contraception (see below) during chemotherapy treatment and for at least six months thereafter.

   Such methods include: (if using hormonal contraception this method must be supplemented with a barrier method, preferably male condom).

   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Intravaginal
     - Transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Injectable
     - Implantable
   - Intrauterine device (IUD)
   - Intrauterine hormone-releasing system (IUS)
   - Bilateral tubal occlusion
   - Vasectomized partner
   - True sexual 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), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.
   - Male condom with spermicide (female condom and male condom should not be used together)

8. ECOG performance status of 0 to 1 (Appendix I).
9. ≥ 18 years of age.
10. Written informed consent obtained prior to any screening procedures and in accordance with federal, local, and institutional guidelines.
11. Patient has exhausted all available treatments, including surgery, and is considered a suitable candidate to receive carboplatin/PLD.

Exclusion criteria:

1. Prior exposure to cumulative doses of doxorubicin >400 mg/m^2 or epirubicin >720 mg/m^2.
2. Confirmed cardiac history of any of the following:
   a) Myocardial infarct within six months prior to registration,
   b) New York Heart Association Class II or worse heart failure (Appendix II),
   c) A history of familial long QT syndrome,
   d) Clinically significant pericardial disease,

e) Electrocardiographic evidence of acute ischemia,

f) Symptomatic atrial or ventricular arrhythmias not controlled by medications,

g) QTc $\geq$ 480 msec calculated from a single ECG reading or a mean of 3 ECG readings using Fridericia's correction (QTcF = QT/RR0.33),

h) Bradycardia (< 40bpm),

i) Left ventricular ejection fraction (LVEF) < the institution lower limit of normal as assessed by ECHO.

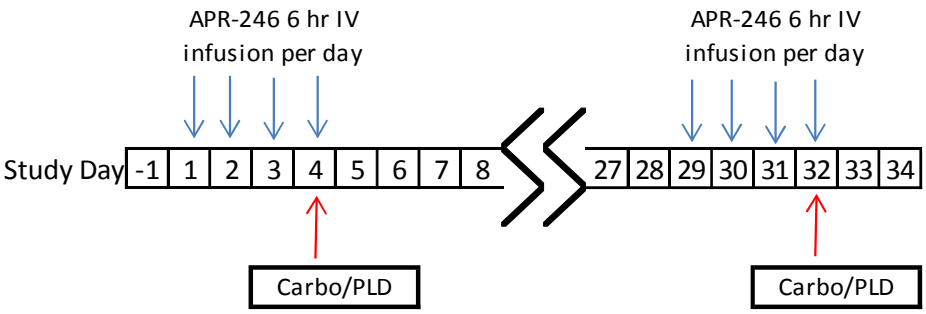
3. Major abdominal surgery or peritonitis within six weeks prior to study treatment.
4. Unresolved bowel obstruction, sub-occlusive disease or the presence of brain metastases.
5. History of uncontrolled allergic reactions to carboplatin, platinum containing compounds or mannitol and/or hypersensitivity to PLD or to any of the excipients.
6. Unable to undergo imaging by either CT scan or MRI.
7. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, neurological conditions, physical examination or laboratory findings) that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment related complications.
8. Breast feeding.
9. Concurrent malignancy requiring therapy (excluding non-invasive carcinoma or carcinoma in situ).
10. Patients requiring or undergoing concurrent treatment with live vaccines.
11. Patients requiring or undergoing concurrent treatment with phenytoin.
12. Known HIV positive status, active hepatitis B or C status.
13. Is taking any concurrent (or within 4 week prior to registration) anti-cancer therapy, immunotherapy, radiotherapy or any ancillary anti-cancer therapy; or any therapy that is considered to be investigational (i.e., used for non-approved indications(s) and in the context of a research investigation). Supportive care measures are allowed.
14. Patients unable to be regularly followed for any reason (geographic, familiar, social, psychological, housed in an institution e.g., prison because of a court agreement or administrative order). Patients who are dependent on the sponsor/CRO or investigational site as well as on the Investigator.

Test product, dose and mode of administration:

Patients will receive a fixed dose of 4.5 g APR-246 (1.5 g of the dose during first 45 minutes followed by 3 g of the dose during 5 hours 15 minutes) if randomized to Arm A.

In all cycles, APR-246 will be administered as a 6-hour infusion daily for four consecutive days (Study Day 1 to Day 4). Carboplatin and PLD will be administered on Day 4 at the same time as the final infusion of APR-246. Carboplatin followed by PLD administration should commence 2-hours after the start of the APR-246 infusion.

Further administration of APR-246 (repeated in 28-day cycles) will commence three days prior to subsequent chemotherapy cycles, with the fourth dose administered the same day as the chemotherapy.



Treatment Administration for Patients Receiving APR-246 (Arm A)

Duration of treatment:

Patients will receive up to six 28-day cycles of the carboplatin/PLD chemotherapy regimen with or without APR-246.

Reference therapy, dose and mode of administration:

Patients randomized to Arm B will not receive APR-246.
Carboplatin and PLD will be administered on Day 1 as per hospital practice. Cycles will be repeated every 28 days for up to six cycles.

Criteria for evaluation:
Efficacy: Patients with measurable disease will be assessed using RECIST (v1.1) criteria and GCIG CA-125 Criteria.

Safety: AEs will be collected throughout the study, from informed consent until 30 days after the last administration of study treatment. AEs will be graded according to NCI CTCAE version 4.0. Serious adverse events (SAEs) will be reported according to Directive 2001/20/EC and 2005/28/EC and the ICH GCP guidelines.

Sample size calculation:
The phase II portion of this study has a flexible sample size. The purpose is to use a smaller sample size with very small or very large observed effect sizes, and a larger sample size where observed effect sizes are promising but more data are needed. For small observed effect sizes (with typically smaller sample sizes), the study results will have traditional phase II interpretations. However, for moderate/large observed effect sizes (with potentially larger sample sizes), the design is intended to provide sufficient evidence to justify regulatory conditional approval.

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BICR	Blinded Independent Central Review
BW	Body weight
CA-125	Cancer Antigen 125
CD	Candidate Drug
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximal Plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOC	Epithelial Ovarian Cancer
FDA	U.S. Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HGSOC	High Grade Serous Ovarian Cancer
HL	Hy's Law
HR	Hazard Ratio
IB	Investigator's Brochure
IC_{50}	Inhibitory Concentration 50%
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
IWRS	Interactive Web Response System
LBM	Lean Body Mass
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHRAUK	Medicine and Healthcare Products Regulatory Agency
MQ	Methylene Quinuclidinone
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
OS	Overall Survival
PARP	Poly (adenosine diphosphate [ADP]) Ribose Polymerase
PD	Progressive Disease
PFI	Platinum-free Interval
PFS	Progression-free survival
PH2RD	Phase II Recommended Dose
PHL	Potential Hy's Law
PiSARRO	P53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer
PLD	Pegylated Liposomal Doxorubicin
PPE	Palmar-Plantar Erthyrodysesthia
PPoS	Predicted Probability of Success
PR	Partial Response
PRIMA	p53 Reactivation and Induction of Massive Apoptosis
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SaOS-2	Osteosarcoma Cell Line
SD	Stable Disease
TEAE	Treatment-emergent Adverse Event
Tid	Three Times Daily
ULN	Upper Limit of Normal
ULRR	Upper Limit of Response Range
US	United States
WBC	White Blood Cell Count

WHO	World Health Organization
Wt	Wild Type

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

APR-407 PiSARRO: p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin/Pegylated Liposomal Doxorubicin Combination Chemotherapy With or Without APR-246.

1.2 Sponsor

This study is being Sponsored by Aprea Therapeutics AB.

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1.5 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will review and evaluate safety data and reports on cumulated serious adverse events (SAEs). Based on this review the IDMC should provide

recommendations to the Sponsor regarding the ongoing scientific and ethical integrity of the study and in reference to the study protocol. The members of the IDMC serve in an individual capacity and provide their expertise and recommendations. The IDMC Charter will outline the roles and responsibilities and serve as the Standard Operating Procedure (SOP) for the IDMC.

The safety and well-being of the trial participants are the most important considerations and should prevail over the interests of the science and society.

2.0 INTRODUCTION AND RATIONALE FOR THE STUDY

2.1 Background Information

2.1.1 General Information

Aprea Therapeutics AB was founded in 2003 by the inventors, Klas Wiman, Galina Selivanova, Vladimir Bykov, Staffan Strömblad, Wenjie Bao and Natalia Issaeva together with Karolinska Innovations AB. The company is aiming to develop target specific drugs for the treatment of cancer by restoration of p53 function. Such treatment should induce massive apoptosis and thus eliminate the tumor.

The company has identified molecules that via p53-dependent pathways induce apoptosis in cancer cells with mutant or wild type p53. Aprea Therapeutics AB has since its inception confirmed the data in house and has screened for novel substances. The compound APR-246 has been selected as the company's first candidate drug (CD).

2.1.2 The p53 Protein and APR-246

P53 was discovered in 1979 as a cellular protein that forms a complex with the viral large T protein in SV40-infected cells. Later studies showed that p53 was a tumor suppressor which could inhibit cell growth and trigger cell death by apoptosis. TP53, the p53 gene is mutated in almost half of all human tumors. The p53 status of a tumor may have a strong impact on sensitivity to commonly used anti-cancer drugs and radiotherapy [1]. Thus, p53 is an important clinical marker and also a novel therapeutic target. In contrast to other tumor suppressor genes, TP53 is typically inactivated by single missense mutations, which is accompanied by loss of the remaining wild type allele. As a rule, mutant p53 proteins are deficient for specific DNA binding suggesting that DNA binding and transcriptional regulation of target genes are critical functions for p53-mediated tumor suppression [2].

The fact that TP53 is mutated in around 50% of human tumors, that mutant p53 protein usually accumulates at high levels, and that mutant p53-expressing tumors respond poorly to conventional therapy makes mutant p53 an attractive target for novel cancer therapy [3]. In hematological malignancies, between 5 and 20% of the patients carry a TP53 mutation in their malignant cell clone. However, for the current indication more than 95% of patients with High Grade Serous Epithelial Ovarian Cancer (HGSOC) carry TP53 mutations [4].

Recent studies have demonstrated that restoration of p53 in p53-deficient mouse tumors triggers rapid and efficient elimination of the tumor through cell cycle arrest, senescence and/or apoptosis [5]. This supports the idea that pharmacological reactivation of p53 should allow efficient elimination of tumors with minimal effects on normal cells.

The small molecule PRIMA-1 (later denoted APR-017) was identified in a cellular screen for compounds that preferentially induce apoptosis in human tumor cells expressing exogenous mutant p53. Optimization of APR-017 resulted in the structural analogue APR-246, the IMP for this study. Treatment with APR-246 has been shown to restore sequence specific DNA binding wild type

conformation and transcriptional transactivation to mutant p53 protein. Furthermore, APR-246 has been shown to synergize with the DNA damaging anti-cancer agents, including platinum compounds and doxorubicin (See IB).

2.2 Disease Background

Ovarian cancer is the seventh most commonly diagnosed cancer among women in the world, accounts for an estimated 239,000 new cases and 152,000 deaths worldwide annually [6]. Ovarian cancer has been of considerable interest to clinical cancer investigators due to the fact that it is among the most chemosensitive of all solid tumors [7]. It is frequently platinum sensitive initially and even in advanced disease the accepted management is a combination of surgery and platinum based chemotherapy.

Despite the evolution of surgical techniques and ever improving chemotherapy regimens, relapse and consequential disease progression remains the most challenging task. Screening has not yet proven an effective tool to diagnose patients at an earlier stage in their disease and late diagnosis is associated with relapse and death after repeated treatment cycles. The 5 year survival rate remains poor at less than 40% and this has remained unchanged for the last 20 years [6]. Thus, there is a need for improved treatment of relapsed ovarian cancer. The combination of carboplatin and pegylated liposomal doxorubicin is widely used in Europe following results of the multicenter phase III CALYPSO study which demonstrated non-inferiority of this combination over the standard carboplatin and paclitaxel combination arm in terms of PFS (11.3 months versus 9.4) with lower rates of severe and long-lasting side effects [8].

Despite rapid scientific advances in the last decades, it has proved difficult to improve outcomes beyond platinum-based therapy introduced in the late 1970s. Cisplatin, and subsequently carboplatin has been combined with other agents, especially taxanes to form the backbone of current treatment regimes. The combination is effective in first-line, platinum sensitive ovarian cancer, but unfortunately since most patients are diagnosed late, recurrence is common. Drug resistance does eventually develop due to repeated treatment with the same drugs. With each relapse, the response to treatment decreases with lower quality of life.

The median survival time for patients with advanced HGSOC is approximately 44 months. In platinum-sensitive cancer, tumor response to first line platinum-based treatment lasts at least 6 months following initial treatment. In the first line setting, carboplatin, generally in combination with a taxane provides impressive results with about a 70% response rate. Patients are retreated at relapse with platinum unless the cancer is platinum resistant (i.e. tumor progression within 6 months after completing first line treatment). Unfortunately almost 50% of Epithelial Ovarian Cancer (EOC) patients will relapse within 18 months and 75% by 30 months. The likelihood that a patient will respond to the reintroduction of a platinum-based regimen depends on the platinum-free interval (PFI), defined as the interval between the last dose of platinum and the time of relapse. Thus, fewer patients with a PFI of 6–12 months are expected to respond to the reintroduction of platinum-based chemotherapy, compared with patients with a PFI of 18–24 months.

As the majority of patients with advanced ovarian cancer will eventually relapse with incurable and terminal disease, there is significant unmet need for improved tools to aid earlier diagnosis and also

for establishing more effective alternative treatment options for the late stage resistant patient population. As such, there is a need for better first-line therapies that may delay or prevent relapse and improve survival rates. An unmet need also exists in the setting of recurrent disease, where currently used therapies have little impact on survival. As such the addition of a new drug on the market to current standard of care may impact significantly on patient management, given the current lack of effective treatment options once patients relapse.

High Grade Serous Ovarian Cancer (HGSOC) accounts for approximately 70% of malignant ovarian surface epithelial carcinoma in Europe and North America [9]. Mutant TP53 is a hallmark of HGSOC, resulting in deregulation of cell cycle checkpoints and uncontrolled tumor cell proliferation and thus represents a key driver event. Pathogenic TP53 mutations have been quoted as occurring in up to 96% of patients with HGSOC [4]. Rearrangements in TP53 have been shown to correlate significantly with resistance to chemotherapy, early relapse and shortened overall survival.

Almost 90% of HGSOC initially present as advanced-stage (stage III of IV) disease [10] thus spreading outside the pelvic cavity hence accounting for low median survival times. There is a need for improved treatment of HGSOC since present therapies have little impact on survival. APR-246 may offer such an opportunity since it has been shown to induce apoptosis and cell death in cancer cells with mutant or otherwise non-functional p53, and in addition to display strong synergistic anticancer effects in combination with several conventional chemotherapeutic drugs including platinum drugs and doxorubicin.

2.3 Choice of Patient Population

The study population will include patients with platinum sensitive recurrent TP53 mutated HGSOC (defined as those patients whose cancer recurs after more than 6 months, but less than 24 months since completion of platinum-based chemotherapy), who in the Investigator's opinion require further treatment with combination carboplatin/PLD systemic chemotherapy (stage III-IV). Relapse should be verified radiologically and/or by CA-125 using Gynecological Cancer Intergroup (GCIG) criteria.

2.4 Investigational Medicinal Product

APR-246, 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo [2,2,2] octan-3-one is also called PRIMA-1^{Met} in the literature, where PRIMA is an acronym for p53 reactivation and induction of massive apoptosis (see IB).

The APR-246 compound has a molecular weight of 199.24 g/mol, is a racemic mixture and is isolated as a white powder. The structure of APR-246 can be seen in Figure 1 below.

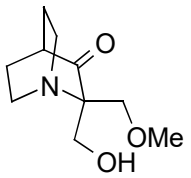

Figure 1. Structure of APR-246

The IMP should be stored at 2-8°C. The IMP is a concentrated solution which should be diluted with sterile 0.9% NaCl solution for infusion before administration. The solution for infusion should be prepared with the prescribed dosage for each patient in accordance with the protocol and separate technical instruction. After preparation of the ready to use solution for infusion the pH of the solution will range from slightly above 4 up to approximately 4.8, depending on dosage. The infusion will be slightly hypertonic. The prepared APR-246 study product is to be stored at not more than 25°C. The infusion to the patient should be finalized within 24 h from the time of preparation.

APR-246 is a prodrug that is converted to the active compound methylene quinuclidinone (MQ), responsible for the anticancer effects of APR-246. Ample evidence shows that APR-246 in physiological conditions is converted to MQ, which has been shown to bind to cysteines in mutant unfolded p53 pushing the protein towards a functional wild type conformation.

2.5 Preclinical Studies

Please refer to the IB for full details.

2.5.1 Primary Pharmacology of APR-246

APR-246 has demonstrated efficacy in various preclinical *in vitro*, *ex vivo*, and *in vivo* cancer models, as single substance as well as in combination with several conventional chemotherapeutics. In many of these models APR-246 has shown good potency and efficacy and unique pharmacological profile in comparison with conventional chemotherapeutic drugs.

APR-246 reduced cell viability in a dose-dependent manner being more potent in SaOS-2-His273 cells, expressing mutant p53 than in TP53 null cells (lacking p53 expression). It also reduced cell viability in a large number of other cancer cell lines with different TP53 status. In *ex vivo* experiments with primary cancer cells from patients with acute myeloid leukemia (AML) and ovarian cancer, APR-246 reduced cell viability and, in contrast to conventional drugs, was effective also in TP53 mutant cancer cells.

A large number of solid cancer cell lines with various cisplatin sensitivity and TP53 status, were investigated in combination studies with APR-246 and cisplatin. In the various resistant cell lines tested, platinum compounds and doxorubicin showed resistance while the sensitivity for APR-246 was considerably less affected. Strong synergistic (CI<0.5) effects with APR-246 were observed in all cell lines with homozygous hotspot TP53 mutations. These cell lines showed high levels of

mutant p53 protein. Synergistic (CI<0.8) or strong synergistic (CI<0.5) effects were observed in cancer cell lines with frequently occurring TP53 mutations accumulating moderate levels of mutant p53. Variable rather than strong synergistic combination effects were observed in the cell lines with wild type (wt) p53 and in those in which full length p53 protein is not detectable.

These results are consistent with the proposed dual mechanisms of action of APR-246, and show that APR-246 can exert anticancer effects both in cells carrying wt p53 and cells carrying mutant p53. Hence, both p53 dependent and independent apoptotic effects contribute to APR-246 efficacy.

Strong synergistic effects were also observed with APR-246 and cisplatin in the OVCAR-3 cell line, a cisplatin-resistant ovarian carcinoma cell line, carrying the TP53 hotspot mutation R248Q. APR-246 resensitized the OVCAR-3 cancer cells to cisplatin as well as to the anthracycline doxorubicin; the IC_{50} value of cisplatin was decreased 5-fold.

Strong synergistic effects of APR-246 and the DNA-damaging compound doxorubicin were also seen in the doxorubicin-resistant A2780ADR ovarian cancer cell line.

Strong synergy between cisplatin and APR-246 was furthermore shown in a number of primary cancer cells from ovarian cancer patients.

An additive, close to synergistic effect (CI=0.82) in terms of antitumor efficacy was observed with APR-246 in combination with cisplatin in a xenograft study using the A2780-CP20 cell line, an aggressively growing cisplatin-resistant TP53 mutant ovarian cancer cell line. *Ex vivo* immunohistochemical analysis of the tumors showed an increase of active caspase-3 positive cells confirming that APR-246 induced apoptosis.

2.5.2 Safety Pharmacology of APR-246

REDACTED

REDACTED

2.5.3 Pharmacokinetics

REDACTED

2.5.4 Toxicology

REDACTED

2.6 Previous Clinical Studies

The first clinical trial (APR-246-01) was conducted with APR-246 in patients with refractory hematological malignancies and prostate cancer. For further information please refer to the IB.

2.7 Rationale for the Current Study

HGSOC accounts for approximately 70% of malignant surface epithelial carcinoma in Europe and North America [9]. Clinical data shows that TP53 mutations are present in at least 96% of patients with HGSOC [4]. Furthermore, TP53 mutations have been shown to correlate significantly with resistance to chemotherapy, early relapse and shortened overall survival [11].

Despite the evolution of surgical techniques and ever improving chemotherapy regimens, relapse and consequential disease progression remains the most challenging task for ovarian cancer patients. The combination of carboplatin and pegylated liposomal doxorubicin has shown an improvement in PFS (11.3 months versus 9.4) with lower rates of severe and long-lasting side effects, and has been accepted as standard of care for patients with platinum-sensitive ovarian cancer, including HGSOC [8].

APR-246 may offer an opportunity to improve current treatment of HGSOC. The rationale for this derives from preclinical evidence that APR-246/MQ (i.e., the active moiety of APR-246) induces apoptosis and cell death in cancer cells with mutant or otherwise non-functional p53. Additional to the apoptosis-inducing effect as a single substance, APR-246 can act synergistically with platinum compounds by reversing the cisplatin sensitivity of cisplatin-resistant TP53 mutant ovarian cancer cell lines, resulting in resensitization of cancer cells to cisplatin.

The completed Phase I/II extended exposure study of single agent APR-246 (APR-246-01 Amendment 6) indicated that prolonged exposure, after 4-hour and 6-hour pulse incubations as compared to 2 hours, resulted in stronger apoptotic response. Ten patients have received 6-hour infusions and pharmacokinetic, safety and efficacy parameters have been collected. No major safety concerns were reported, and 2 patients have shown protocol defined clinical responses.

This study also provided important information about APR-246 and increased knowledge about its safety and tolerability, as well as pharmacokinetic (PK) and optimal administration. In summary, the results of the extension study suggested that the adapted dose regimen was suitable and that APR-246 was well tolerated with limited number of adverse events. The pharmacokinetic data suggested time-independent and dose-independent kinetics.

In view of the data accumulated, the starting dose for the PiSARRO study at Cohort 1 was 35.0 mg/kg/day (approximately 50% of the PH2RD (Phase II recommended dose) dose of 67.5 mg/kg/day) for 6-hours on Days 1 to 4 with carboplatin AUC 5 and PLD 30 mg/m^2 on Day 4 within Phase Ib of the planned clinical study.

The purpose of this study is to determine whether patients with platinum sensitive, recurrent, HGSOC with TP53 mutations causing overexpressed defect p53 protein, will benefit from treatment with APR-246 in combination with the reintroduction of a platinum-based regimen. Focus will be on patients with HGSOC with recurrent disease at least 6 months and up to 24 months after platinum based treatment.

The objectives of the Phase Ib were to find the maximum tolerated dose of APR-246 in this combination, to determine PK variables, to follow appropriate biomarkers, and safety.

The Phase II portion of the study is an open-label randomized evaluation of APR-246 in combination with a carboplatin/PLD chemotherapy regimen, versus carboplatin/PLD chemotherapy regimen alone in patients with HGSOC with TP53 mutation and recurrent disease at least 6 months and up to 24 months after platinum based treatment. Antitumor activity will be determined by a CT scan/MRI using RECIST v1.1 criteria and with CA-125 using the GCIG criteria. Patients will be followed to progression.

2.7.1 Preliminary Results from the Current Study, Phase Ib, and Rationale for Selected Dose for Phase II Study

The first phase of this study was designed to determine the dose for the second (randomized) phase of the study. In this phase APR-246 was administered IV in combination with carboplatin and PLD at 3 dose levels; 35 mg/kg, 50 mg/kg and 67.5 mg/kg, to 27 women with high grade serous ovarian cancer, previously treated with platinum-based antineoplastic agents. Each treatment cycle was repeated every 28 days to a maximum of six treatment cycles.

The primary study objectives were an assessment of safety and tolerability and an evaluation of the pharmacokinetics of APR-246 in combination. In this first phase of study APR-407, primary study end points were dose-limiting toxicity and a safety assessment of the combined APR-246 and carboplatin PLD combination together with limited pharmacokinetic profiles.

At the data cut-off point of 12 May 2016, the most commonly reported adverse events were neutropenia, dizziness, nausea, vomiting, headache, dysgeusia, constipation, diarrhea, depressed appetite, anemia, thrombocytopenia device occlusion, mucosal inflammation, pyrexia, and abdominal pain. This pattern of toxicity, except for the bone marrow suppression, was similar to that reported following treatment with APR-246 alone in study APR-246-01.

There is no evidence of a pharmacokinetic interaction between APR-246 and carboplatin or PLD and no evidence of consistent QTc prolongation at any of the explored dose levels.

2.7.1.1 Rationale for a Selected Dose of APR-246

REDACTED

REDACTED

2.7.2. Quality of Life Assessment and Rationale for the Selection of the Questionnaires

The EORTC QLQ-C30 (including the Ovarian Module QV28) Quality of life (QoL) assessment was chosen as it may help determine the intermediate- and long-term effects of protocol treatments whereas the FACT-O questionnaire was selected in order to determine the impact of the study treatments on the emotional, social/family and functional well-being of the patients.

2.8 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.
2. Detailed electronic Case Report Forms (eCRFs) will be completed for every patient.
3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.

4. Requirements for informed consent in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.
5. Safety data will be recorded and evaluated.
6. Routine monitoring visits will be conducted by the Sponsor's representative (Theradex®) to ensure data accuracy.
7. APR-246 accountability will be strictly maintained.
8. This trial will be conducted according to Good Clinical Practice (GCP), the protocol and applicable regulatory requirements.

3.0 TRIAL OBJECTIVES AND ENDPOINTS

3.1 Objectives and Endpoints

3.1.1 Primary Objective

- To assess the efficacy of a combined APR-246 and carboplatin/PLD chemotherapy regimen in patients with platinum sensitive recurrent HGSOC with mutated TP53.

3.1.2 Secondary Objectives

- To assess the safety profile of the combined APR-246 and carboplatin/PLD chemotherapy regimen compared with carboplatin/PLD chemotherapy regimen alone.
- To evaluate potential biomarkers.
- To assess the biological activity in tumor and surrogate tissues.
- To compare quality of life of patients treated with these regimens.

3.1.3 Primary Endpoint

- Progression-free survival (PFS) based on Blinded Independent Central Review (BICR) is the primary endpoint and is defined as the number of days from the date of randomization to the date of objective disease progression or relapse (according to RECIST v1.1 only) or death due to any cause, whichever occurs first. If neither event occurs, PFS will be censored at the date of the last evaluable tumor assessment. Symptomatic deterioration is not objective disease progression.

3.1.4 Secondary Endpoints

Secondary endpoints include the following:

- Best overall response and overall response rate (according to RECIST v1.1 and GCIG Criteria)
- Duration of response (complete or partial response)
- PFS by assessment of CA-125 (according to GCIG Criteria)
- Overall survival
- Safety profile based on AEs and laboratory assessments
- Evaluation of biomarkers and tumor activity based on CA-125
- Quality of Life assessment using EORTC Ovarian (QLQ-30 and QLQ-OV28) and the Functional Assessment of Cancer Therapy-Ovarian (FACT-O)

Tumor response data will be summarized at each tumor assessment cycle using the following response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE). Best overall response for a patient is the best

response recorded from the start of the treatment until disease progression or death. Best overall response will be summarized as the number (%) of patients in each category of response (CR, PR, SD, PD, and NE). PR and CR must be confirmed by a repeat assessment at least 28 days after the criteria are first met for the response to be considered a PR or CR.

The overall response rate is defined as the percentage of patients with a confirmed response of CR or PR in a given population.

The duration of response (confirmed CR or PR) is defined as the number of days from the date of initial response (not the confirmation date) to the date of objective disease progression or death due to any cause, whichever occurs first. If neither event occurs, duration of response will be censored at the date of the last evaluable tumor assessment. Symptomatic deterioration is not objective disease progression.

Overall survival (OS) is defined as the number of days from the date of randomization to the date of death. In the event of no death, overall survival will be censored at the last known alive date.

4.0 STUDY DESIGN

4.1 Overview of Study Design

This study is an open-label, multi-center Phase II proof-of-concept study with a dose confirmation component to assess whether patients with platinum sensitive recurrent TP53 mutated high grade serous ovarian cancer (HGSOC) will benefit from treatment with APR-246 in combination with a carboplatin/PLD chemotherapy regimen. It is planned that patients will receive up to 6 cycles of treatment.

Archived sections from the original tumor sample will be reviewed by a gynecological pathologist to confirm the diagnosis of HGSOC and positive IHC staining for p53 (please refer to the laboratory manual). Patients without positive p53 staining will not be included.

Patients will be randomly assigned in a 1:1 ratio to receive either:

- Arm A: APR-246 with the carboplatin/PLD chemotherapy regimen,
- Arm B: Carboplatin/PLD chemotherapy alone.

Optional frozen/fixed core biopsies will be undertaken after randomization, but prior to any infusion, on day 1 for all patients and day 3 in APR-246 patients.

The study will enroll up to 400 patients with positive IHC staining for p53. A CT scan/MRI using RECIST v1.1 criteria will be performed at pre-treatment, after 2 cycles (8 weeks), 4 cycles (16 weeks) and after the last cycle (24 weeks).

At subsequent follow-up visits, tumor assessments by CT scan/MRI will be performed 2 months (± 2 weeks) after the end of treatment visit and every 3 months (± 2 weeks) thereafter, until the documented disease progression, as determined by the Investigator at each site and defined by RECIST v1.1.

All scans for each individual patient should have the same modality (CT or MRI) but CT is preferred.

4.2 Randomization/Registration of Patients

Upon completion of all screening evaluations, the center will register the patient using the Interactive Web Response System (IWRS). After successful completion of patient registration, a treatment assignment and randomization number will be issued.

Once the patient is registered through the IWRS, the patient is considered enrolled in the study. Specific instructions for the central enrolment and registration procedures are provided to the center in the Study Operations Manual.

Registered patients will be assigned a unique patient identifier number. If a patient is withdrawn and replaced (as described in Section 13), the patient identifier number will not be reused.

4.3 Shipment of p53 Samples

All archived pathology samples will be sent for centralized p53 analysis after registration and following local analysis. Labeling and shipment procedures will be provided in a separate Laboratory Manual.

4.4 Treatment Allocation

Patients will be randomized in a 1:1 ratio to receive the carboplatin/PLD chemotherapy regimen with or without APR-246. The study treatment will not be blinded. Patients will be registered on-study as described in Section 4.2; the treatment arm will be automatically allocated during registration.

4.5 Drug Products

4.5.1 Investigational Medicinal Product, APR-246

The study substance APR-246 (2-hydroxymethyl-2-methoxymethyl-1-azabicyclo [2,2,2] octan-3-one) is isolated as a white powder. APR-246 is prepared from quinuclidin-3-one in one reaction step using formaldehyde in methanol and in the presence of potassium carbonate (see IB). The IMP, APR-246 concentrate for solution for infusion, will be manufactured by Cobra BioPharma, Matfors Sweden.

4.5.2 Reference Products Carboplatin and PLD

Carboplatin and PLD will be supplied by the hospital's pharmacy and will be administered in combination in 28-day cycles for up to 6 cycles.

4.6 Duration of Therapy

Patients will receive up to six 28-day cycles of the carboplatin/PLD chemotherapy regimen, with or without APR-246.

4.7 End of Study

The end of the study is defined as the date of the last visit of the last patient taking part in the study.

4.8 Study Discontinuation by the Sponsor

For reasonable cause, either the Investigator or the Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that warrant termination by the Sponsor include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.

- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements (non-compliance).
- Lack of evaluable and/or complete data.
- Decision to modify the developmental plan of the drug.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

4.9 Treatment Plan for Patients after the Study

It is expected that patients will go on to receive treatment according to usual hospital practice

5.0 SELECTION AND WITHDRAWAL OF PATIENTS

5.1 Inclusion Criteria

To be eligible to participate in this study, patients must meet all of the following inclusion criteria:

1. Archived sections from the original FFPE sample reviewed by a gynecological pathologist confirming High Grade Serous Ovarian Cancer, High Grade Serous Peritoneal Cancer or Primary Fallopian Tube Cancer, and positive IHC staining for p53 assessed according to defined standard (as detailed in the laboratory manual). Cases that do not show p53 staining will not be included.
2. Radiologically-confirmed Disease Progression between six and twenty-four (6-24) months after a first or second platinum based regimen.
3. At least a single (RECIST v1.1) measurable lesion.
4. Adequate organ function prior to registration:
   a) Bone Marrow Reserve:
      - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L,
      - Platelets $\geq 100 \times 10^9$/L,
      - Hemoglobin ≥ 9 g/dL.
   b) Hepatic:
      - Total bilirubin level < 1.5 x ULN,
      - ALT and AST < 2.5 x ULN.
   c) Renal:
      - Calculated creatinine clearance > 30 mL/min.
   d) Electrolytes
      - Potassium within institutional normal ranges.
5. Toxicities from previous cancer therapies, excluding alopecia, must have recovered to grade 1 (defined by CTCAE version 4.0). Chronic stable grade 2 peripheral neuropathy secondary to neurotoxicity from prior therapies may be considered on a case by case basis by the Principal Investigator.
6. If of childbearing potential, negative pre-treatment serum pregnancy test.
7. If of childbearing potential, willing to use an effective form of contraception (see below) during chemotherapy treatment and for at least six months thereafter.

   Such methods include: (if using hormonal contraception this method must be supplemented with a barrier method, preferably male condom).
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Intravaginal

- Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- True sexual 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), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- Male condom with spermicide (female condom and male condom should not be used together)

8. ECOG performance status of 0 to 1 (Appendix I).
9. ≥ 18 years of age.
10. Written informed consent obtained prior to any screening procedures and in accordance with federal, local, and institutional guidelines.
11. Patient has exhausted all available treatments, including surgery, and is considered a suitable candidate to receive carboplatin/PLD.

5.2 Exclusion Criteria

Patients will be excluded if any of the following exclusion criteria are met:

1. Prior exposure to cumulative doses of doxorubicin >400 mg/m^2 or epirubicin >720 mg/m^2.
2. Confirmed cardiac history of any of the following:
   a) Myocardial infarct within six months prior to registration,
   b) New York Heart Association Class II or worse heart failure (Appendix II)
   c) A history of familial long QT syndrome,
   d) Clinically significant pericardial disease**,**
   e) Electrocardiographic evidence of acute ischemia,
   f) Symptomatic atrial or ventricular arrhythmias not controlled by medications,

g) QTc ≥ 480 msec calculated from a single ECG reading or a mean of 3 ECG readings using Fridericia's correction (QTcF = QT/RR0.33),

h) Bradycardia (<40 bpm),

i) Left ventricular ejection fraction (LVEF) < the institution lower limit of normal as assessed by ECHO.

3. Major abdominal surgery or peritonitis within six weeks prior to study treatment.
4. Unresolved bowel obstruction, sub-occlusive disease or the presence of brain metastases.
5. History of uncontrolled allergic reactions to carboplatin, platinum containing compounds or mannitol and/or hypersensitivity to PLD or to any of the excipients.
6. Unable to undergo imaging by either CT scan or MRI.
7. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, neurological conditions, physical examination or laboratory findings) that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment related complications.
8. Breast feeding.
9. Concurrent malignancy requiring therapy (excluding non-invasive carcinoma or carcinoma in situ).
10. Patients requiring or undergoing concurrent treatment with live vaccines
11. Patients requiring or undergoing concurrent treatment with phenytoin.
12. Known HIV positive status, active hepatitis B or C status.
13. Is taking any concurrent (or within 4 week prior to registration) anti-cancer therapy, immunotherapy, radiotherapy or any ancillary anti-cancer therapy; or any other therapy that is considered to be investigational (i.e., used for non-approved indications(s) and in the context of a research investigation). Supportive care measures are allowed.
14. Patients unable to be regularly followed for any reason (geographic, familiar, social, psychological, housed in an institution e.g., prison because of a court agreement or administrative order). Patients who are dependent on the sponsor/CRO or investigational site as well as on the Investigator.

5.3 Withdrawal of Patients and Study Termination

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time without penalty or loss of benefits or other adequate treatments to which he/she is otherwise entitled.

Investigators also have the right to withdraw patients from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the patient, or in the case of lack of co-operation. After withdrawal of a patient, the investigator is responsible for ensuring adequate

treatment and follow-up, although every effort should be made to complete all assessments at an End of Treatment visit as listed in Section 7.0.

Should a patient decide to withdraw after administration of the investigational medicinal product, or should the investigators decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given of why the patient is withdrawing or being withdrawn from the study.

The reason, time, and date for withdrawal must be noted in the eCRF. If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event must be recorded in the eCRF.

Patients who are withdrawn before completion of the first cycle of APR-246, carboplatin and PLD as prescribed will be replaced.

The study treatment will be discontinued at any time if any of the following situations occur; in the case of study termination by the Sponsor patients will be allowed to continue to receive the standard of care:

1. Completed 6 cycles of treatment.
2. Progressive disease per RECIST v1.1 criteria.
3. ≥ Grade 3 APR-246 related toxicity that leads to a delay in dosing and that persists for more than 4 weeks from the last planned study drug administration or recurs after the maximum dose reduction, despite optimal supportive therapy.
4. Patient refusal.
5. Lost to follow-up/noncompliance.
6. Significant illness that can affect the patient's ability to comply with study procedures.
7. At the discretion of the Investigator.
8. Pregnancy.
9. Study termination by Sponsor.

5.4 Compliance with Study Procedures

Patients will receive the study treatment as outlined in Section 6.0. The details of the study treatment will be documented in the eCRF and IMP accountability forms as applicable.

All study treatment related procedures will be performed in the hospital or clinic by qualified health care personnel. All instances of noncompliance and all resulting protocol deviations will be recorded in the eCRF.

6.0 TREATMENT OF PATIENTS

6.1 Drug Supply and Handling Procedures

6.1.1 Investigational Medicinal Product, APR-246

The IMP will be manufactured according to Good Manufacturing Practice (GMP), and labeled according to GCP, GMP and the national requirements for each site. The labels will comply with the legal requirements of the country. They will include storage conditions for the drug but no information about the study.

The IMP will be distributed in vials to the pharmacies of each participating study center. The APR-246 substance will be diluted in 0.9% sodium chloride solution at the appropriate concentration for infusion for each patient.

At the pharmacies, the IMP vials are to be stored at 2-8ºC. At the pharmacies and at the study centers, the prepared APR-246 study product (diluted in sodium chloride solution) is to be stored at not more than 25ºC. The infusion should be completed within 24h from the time of preparation (see Study Manual).

Detailed instructions on vial concentration, preparation and dispensing can be found in the Pharmacy File.

6.1.2 Carboplatin

Carboplatin will be provided from the pharmacy stock. The carboplatin bag used for administration will be labeled according to the local routines and regulatory requirements. The hospital will be responsible for ordering carboplatin. The manufacturer and batch numbers will be documented.

Please refer to the Summary of Product Characteristics for further information on carboplatin.

6.1.3 Pegylated Liposomal Doxorubicin (PLD) Hydrochloride

PLD will be provided from the pharmacy stock. The PLD bag used for administration will be labeled according to the local routines and regulatory requirements. The hospital will be responsible for ordering PLD. The manufacturer and batch numbers will be documented.

Please refer to the Summary of Product Characteristics for further information on PLD.

6.2 IMP Accountability/Disposition of Clinical Trial Supplies

IMP accountability records will be maintained for all clinical trial supplies.

IMP accountability records will be kept at the pharmacy and at the study centers. The pharmacy must maintain accurate records demonstrating date and amount of IMP received, to whom and by whom administered, and accounts of any IMP accidentally or deliberately destroyed.

The Investigator is responsible for keeping records to ensure that:

a. Deliveries of IMPs are correctly received and recorded by a designated person.
b. Study medications are handled and stored safely and properly.
c. Study medications are dispensed only to study patients in accordance with the protocol.
d. All unused medication and empty containers are stored until they have been checked by the study monitor.
e. It is possible to reconcile records of all used and unused stocks as confirmed by the Investigator's signature.

The IMP is the property of Aprea Therapeutics AB and must not be passed on to third parties. Any discrepancies between returned and expected returned IMP should be explained.

6.3 Method of Assigning Patients to Treatment Groups

Up to 400 patients will be centrally registered and randomly assigned study treatment in a 1:1 ratio to receive either:

- Arm A: APR-246 treatment on Days 1 to 4, with carboplatin and PLD administered concurrently on Day 4 (treatment repeated every 28 days for up to six cycles) or
- Arm B: Carboplatin and PLD alone administered on Day 1 of each 28-day cycle, repeated for up to six cycles.

Patients will be stratified at randomization by:

- Platinum-free Interval after previous platinum based regimen. 6-12 months vs. 12-24 months
- Prior Lines of Platinum Treatment. One line vs. Two lines
- BRCA status. known positive vs. other

The schema for the study is shown in Figure 2 below.

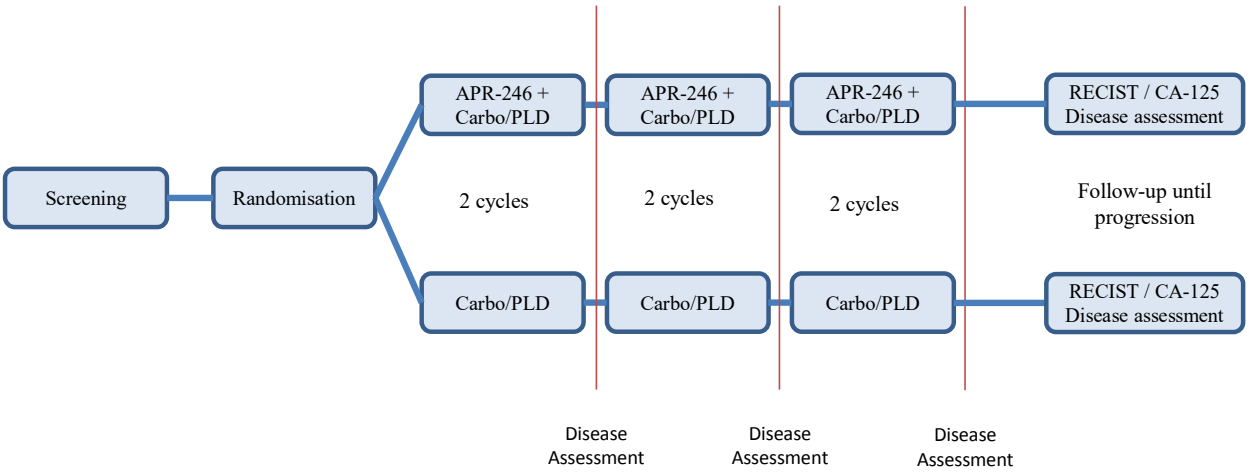

Figure 2. Phase II Schema

6.4 Treatment Administration

6.4.1 Treatment Arm A: APR-246 with carboplatin and PLD

Patients will receive a fixed dose of 4.5 g APR-246 (1.5 g of the dose during first 45 minutes followed by 3 g of the dose during 5 hours 15 minutes) on Days 1 to 4 with carboplatin AUC 5 and PLD 30 mg/m^2 on Day 4 (Figure 3). Carboplatin and PLD administration to be given on Day 4 only should commence 2 hours after the start of the APR-246 infusion. Further administration of APR-246 (repeated in 28-day cycles) will commence three days prior to subsequent chemotherapy cycles, with the fourth dose administered the same day as the chemotherapy.

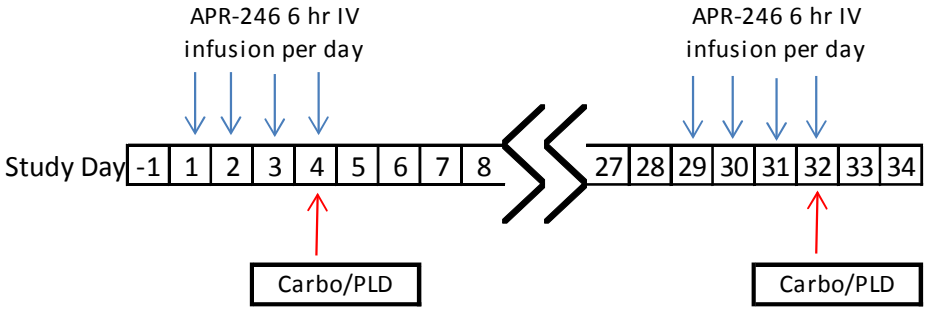

Figure 3. Treatment Administration for Patients Receiving APR-246

Note: The entire dose should be given even if the infusion needs to be extended beyond a total time of 6 hours (e.g. due to slightly larger start volume in prefilled infusion bags).

APR-246 Treatment Duration

Treatment will be repeated every 28 days for up to 6 cycles in the absence of disease progression or unacceptable toxicity. Supportive therapy, including growth factors, can be given as per institutional standard of care.

Carboplatin Dosing

The dose of carboplatin will be calculated as per standard practice at that hospital. Patients will start at carboplatin with an AUC 5.

Pegylated Liposomal Doxorubicin Dosing

The dose of PLD will be calculated based on the body surface of the patients at 30 mg/m^2 as per standard practice at that hospital.

6.4.2 Treatment Arm B: Carboplatin and PLD alone

Patients will receive carboplatin AUC 5 plus PLD at 30 mg/m^2 on Day 1 of each cycle. Treatment will be repeated every 28 days for a total of up to six cycles in the absence of disease progression or unacceptable toxicity. Supportive therapy will be given as per institutional standard of care. Patients randomized to Arm B will not receive APR-246.

Carboplatin Dosing

The dose of carboplatin will be calculated as per standard practice at that hospital. Patients will start at carboplatin with an AUC 5.

Pegylated Liposomal Doxorubicin Hydrochloride Dosing

The dose of PLD will be calculated based on the body surface of the patients at 30 mg/m^2 as per standard practice at that hospital.

6.4.3 Treatment of Adverse Events of the Central Nervous System related to APR-246

If a patient reports any clinical adverse event of any grade during the administration period of APR-246 that could be considered to originate from the central nervous system (e.g. dizziness, vertigo, nausea) then the patient will be given a rescue medication as per the institutional standard of care (Table 1).

Table 1. Rescue Medications for use with APR-246

Indication	Supportive Measure
Central Nervous System symptoms (Treatment and Prevention)	Prochlorperazine 10 mg orally tid [a] or other as per the institutional standard of care Start Day -1 prior to APR-246 administration
Persistent CNS symptoms	Cyclizine 50 mg IM or other as per the institutional standard of care

a. Prochlorperazine 10 mg orally tid (three times daily). To continue until end of Day 4 of the cycle. When used prophylactically for future treatment, start the day prior to the Day 1 administration of APR-246 of each cycle (as needed).

If during the infusion the patient continues to remain symptomatic intramuscular administration of cyclizine 50 mg may be considered.

6.5 Dose Modifications

6.5.1 Modifications for APR-246 due to Adverse Events during Infusion

If a patient in Arm A has any clinical adverse event ≥ grade 3 during the APR-246 infusion, the infusion should immediately be stopped. The type, severity and duration of the adverse event should be carefully assessed as well as the relationship to APR-246.

If the adverse event is considered to be unrelated to APR-246, the infusion may be resumed within 2 hours.

If the adverse event is considered to be related to APR-246, as long as all symptoms resolve to CTCAE Grade 1 or less within 2 hours, the infusion may be resumed.

In case of re-challenge, the infusion should resume at the same infusion rate (the same dose per time unit) as the initial infusion. If no symptoms occur during re-challenge, the infusion can continue until the whole dose is given and the treatment can continue according to the protocol.

If the same symptoms do occur or increase in severity during re-challenge the infusion should be stopped.

If the event lasts longer than 2 hours, then the remainder of the APR-246 infusion for that day should be discarded. If the patient has recovered sufficiently by the next day, the remainder of the planned course should be administered.

After an adverse event considered as related, a single level dose reduction of APR-246 is allowed (Table 2). The rationale for the suggested dose reductions is the steep relation between C_{max} and dose, revealed by modeling based on an extended population PK analysis (Section 2.7.1.1). If more than two dose reductions of APR-246 are required, APR-246 must be discontinued.

The type, severity and duration of the symptoms, adverse event and infusion timings (start and stop) should be carefully documented in the patient's medical charts as per trial procedures.

Table 2. Dose Modifications of APR-246

Dose Modification	APR-246 Dose
Current Dose Level (DL)	APR-246 4.5 g 1.5 g (for first 45 minutes) + 3 g (for 5 hours 15 minutes)
First dose reduction DL-1	APR-246 4.0 g 1.33 g (for first 45 minutes) + 2.67 g (for 5 hours 15 minutes)
Second dose DL-2	APR-246 3.5 g 1.16 g (for first 45 minutes) + 2.34 g (for 5 hours 15 minutes)

The rationale behind this dose reduction scheme is the steep relation between C_{max} and dose, e.g. the suggested 11% and 22% reductions in dose result in 19% and 33% lowering of the average C_{max}, respectively (Section 2.7.1.1).

6.5.1.1 APR-246 Infusion and Systemic Chemotherapy Delays

The days 1 to 4 APR-246 administration, together with the day 4 chemotherapy, are to be regarded as one treatment cycle and must be administered consecutively.

On day 1, prior to APR-246 administration, the hematological status of the patient should be assessed. If the patient has any hematological adverse event that would prevent systemic chemotherapy administration on day 4, the APR-246 infusion and systemic chemotherapy should be delayed until recovery (see Section 6.5.2.1).

If a patient has any adverse event on days 2, 3 or 4 prior to the APR-246 infusion which, in the opinion of the Investigator, would prevent systemic chemotherapy administration, the remainder of the planned APR-246 administration should be stopped. Once the patient has recovered sufficiently to receive chemotherapy, the whole treatment cycle (consisting of days 1-4 APR-246 and day 4 chemotherapy) should be restarted as previously planned.

If APR-246 and/or systemic chemotherapy are delayed, the reasons for delay should be recorded in eCRF.

6.5.2 Dose Modifications for Systemic Chemotherapy

For typical hematological (Table 3 and Table 4) and non-hematological (Section 6.5.2.2) adverse events seen with carboplatin and PLD, the dose modifications specified below should be applied. However, if any adverse events occur that are not typical or that are considered unusual, the Sponsor should be consulted prior to re-treating the patient.

If due to adverse events the patient is unable to continue treatment with PLD, the Investigator may consider continuing with carboplatin monotherapy and APR-246 in Arm A to a total of six cycles (including all prior combination chemotherapy cycles).

If due to adverse events the patient is unable to continue chemotherapy with both PLD and carboplatin, the patient may continue monotherapy APR-246 up to 6 courses in total if the following criteria are met:

- There is CA-125 reduction suggestive of treatment benefit (eligible patients)
- Latest radiological scans shows evidence of response
- Patient is evaluated as not having symptoms suggestive of progressive disease
- The Investigator assessment is that APR-246 monotherapy is of continued benefit to the patient
- APR-246 administration has been approved by the Sponsor.

6.5.2.1 Hematological Toxicity and Dose Modifications

The absolute neutrophil count (ANC) must be ≥1.50 x 10^9/L and the platelet count must be ≥100 x 10^9/L in order to administer full doses of carboplatin and PLD in each cycle as assessed on day 1. In the event of an ANC < 1.0 x 10^9/L, hematological assessment should be performed twice a week until recovery of ANC to >1.0 x 10^9/L. Patients should be monitored prior to each dose for platelet and neutrophil counts, and at the discretion of the Investigator, if necessary, the dose of carboplatin and/or PLD may be either reduced or withheld in the presence of hematological toxicity according to the following scale (Table 3):

Table 3. Dose Modification of Systemic Chemotherapy for Hematological Toxicities

Hematological Assessment on Day 1 of a Cycle:			
ANC (x 10^9 /L)		**Platelet Count (x 10^9 /L)**	**Dose Modification**
≥1.5	and	≥100	Administer full dose of Carboplatin and PLD
<1.5	and/or	<100	Delay cycle for 7 days. If within normal acceptable parameters (as above) proceed with dose reductions of carboplatin to AUC 4 and PLD 25 mg/m^2.
Dose reduction to carboplatin AUC 4 and PLD 25 mg/m^2 is also required in the following circumstances: • ANC < 0.5 x 10^9 /L for > 7 days • An episode of febrile neutropenia (temp ≥ 38.5°C and ANC < 1.0 x 10^9 /L) • Platelets < 25 x 10^9 /L, or bleeding requiring a platelet transfusion			

Growth factors:

- For patients who have a prolonged neutropenia, Investigators may administer growth factors to aid white cell count recovery. This should be given per the package insert.
- Patients who the Investigator considers to be at risk for developing neutropenia (considering bone marrow tolerance with prior chemotherapy or neutropenia while on the PiSARRO study)

that could affect their ability to receive study treatment per the study protocol, should consider administering prophylactic growth factor per the package insert.

For patients in Arm A:

- If hematological recovery is inadequate by Day 42 of any cycle, the Investigator should discuss appropriate patient management with the Sponsor before allowing the patient to continue with study drug treatment. If the patient is showing signs of response, the Investigator may retain the patient in the study, but should assess the potential for further prolonged periods of marrow suppression and the associated adverse events as part of this decision process.
- In the event that a patient requires a second dose reduction of systemic chemotherapy or the initial recovery of hematologic parameters took longer than 14 days even with growth factor support, the Investigator may also consider a single level reduction in the dose of APR-246 in conjunction with a further dose reduction of chemotherapy per Table 4.

Table 4. Dose Modification of Systemic Chemotherapy for Hematological Toxicities in Arm A

Chemotherapy Modification	Treatment Delay	APR-246 Dose Modification
Initial Dose Reduction	Less than 14 days	None
	14 days or more	Reduce one level
Second Dose Reduction	Any	Reduce one level

For patients in Arm B:

- If hematological recovery is inadequate by Day 42 of any cycle after cycle 2, the Investigator should discuss appropriate patient management with the Sponsor.

6.5.2.2 Non-Hematological Toxicity

Please see relevant sections below for specific management.

Patients unable to be dosed within 4 weeks of scheduled therapy should be discussed with the Sponsor to decide if to still proceed in the study.

6.5.2.2.1 Renal Impairment

The carboplatin dose should be calculated based on GFR. If renal function drops less than 20 mL/min, the patient should be discontinued from treatment with carboplatin.

Dose modifications should not be required for PLD in patients with renal impairment.

6.5.2.2.2 Hepatic impairment

PLD can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 x the upper limit of the normal range. See Table 5 below.

Carboplatin: Transient increases in liver enzymes have been seen although no dose reduction is usually required. In severe hepatic dysfunction consider a dose reduction after discussing with the Sponsor.

Table 5. Dose Modification of PLD for Hepatic Impairment

Total bilirubin (mg/dL)	Total bilirubin (µmol/L)	PLD Dose
< 1.2	<20.52	100%
1.2 - 3.0	20.52 – 51.3	75%*
>3.0	> 51.3	50%*

*If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for the next cycle can be increased to the next dose level, i.e., if reduced by 25% for the first dose, increase to full dose for cycle 2; if reduced by 50% for the first dose, increase to 75% of full dose for cycle 2. The dosage can be increased to full dose for subsequent cycles if tolerated.

6.5.2.2.3 Cutaneous Toxicity (Palmar-Plantar Erthyrodysesthia (PPE))

Treat symptoms accordingly. Follow dosing guideline as per Table 6.

Table 6. Dose Modification of PLD for Cutaneous Toxicity

	Time after prior PLD Dose		
Toxicity Grade at Current Assessment	**After Day 28 (week 4)**	**Days 35 and 42 (week 5)**	**> Day 42 (week 6)**
Grade 1	**Redose unless** patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	**Redose unless** patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	**Decrease dose by 25 %; return to 4 week interval**
Grade 2	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25 %; return to 4 week interval**
Grade 3	**Wait an additional week**	**Wait an additional week**	**Stop PLD**
Grade 4	**Wait an additional week**	**Wait an additional week**	**Stop PLD**

Grade 1 - mild erythema, swelling, or desquamation not interfering with daily activities
Grade 2 - erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter
Grade 3 - blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing
Grade 4 - diffuse or local process causing infectious complications, or a bedridden state or hospitalization

6.5.2.2.4 Stomatitis

Refer to Table 7. If delay has been necessary due to stomatitis, a change of cycle interval to five weeks is allowed if the Investigator judges it to be in the patient's best interests.

Table 7. Dose Modification of PLD for Stomatitis

	Time after prior PLD Dose		
Toxicity Grade at Current Assessment	**After Day 28 (week 4)**	**Days 35 and 42 (week 5)**	**> Day 42 (week 6)**
Grade 1	**Redose unless** patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	**Redose unless** patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	**Decrease dose by 25 %; return to 4 week interval**
Grade 2	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25 %; return to 4 week interval**
Grade 3	**Wait an additional week**	**Wait an additional week**	**Stop PLD**
Grade 4	**Wait an additional week**	**Wait an additional week**	**Stop PLD**

Grade 1 - painless ulcers, erythema, or mild soreness
Grade 2 - painful erythema, edema, or ulcers, but can eat
Grade 3 - painful erythema, edema, or ulcers, but cannot eat
Grade 4 - requires parenteral or enteral support

6.5.2.2.5 Other Grade 3 or 4 Non-hematological toxicities

Table 8. Other Grade 3 or 4 Non-hematological Toxicities

Grade 3 toxicity (except nausea & vomiting)	Reduce dose of PLD to 20 mg/m^2 and/or reduce dose of carboplatin to AUC 4 provided toxicity has resolved to ≤ Grade 1. If further toxicity occurs, an additional reduction may be made after discussion with Sponsor
Grade 4 toxicity (except nausea & vomiting)	Withhold treatment and discuss with Sponsor

6.5.3 Hypersensitivity / Adverse Drug Reactions to Chemotherapy Agents

All patients will be carefully monitored for clinical features of hypersensitivity reactions. Should a hypersensitivity reaction to carboplatin occur during infusion, this must be discontinued and an attempt at desensitization may be made subsequently if deemed appropriate by the Investigator in discussion with the patient. The timing of this will be at the discretion of the Investigator depending on the initial dose of carboplatin received.

Desensitization should be performed according to local practices and monitoring.

The desensitization procedure should take place with resuscitation facilities within easy access with regular observations and a trained nurse present throughout administration of APR-246 and chemotherapy. If at any point during the dose escalation allergic signs or symptoms are apparent, the carboplatin infusion must be discontinued.

All subsequent cycles should then be given using this procedure.

If it is not possible for the patient to continue to receive carboplatin due to unmanageable hypersensitivity, the Investigator in consultation with the Sponsor can consider either to remove the patient from the study or change to cisplatin monotherapy. Cisplatin monotherapy will be administered in place of the combination chemotherapy on day 4 of all remaining treatment cycles, up to a maximum of 6 cycles (including prior combination chemotherapy).

The cisplatin monotherapy should be administered, monitored and modified according to the local practices at the investigational site.

6.5.4 Cardiac Safety Monitoring in relation to Treatment with PLD

Whenever cardiomyopathy is suspected, i.e., the left ventricular ejection fraction (LVEF) has substantially decreased relative to pre-treatment values and/or LVEF is lower than a prognostically relevant value (e.g., < 45%), the benefit of continued therapy must be carefully evaluated against the risk of developing irreversible cardiac damage. Cardiology consultation is recommended.

6.5.5 Action to be taken in the Event of QT/QTc Prolongation

Although the risk of QT/QTc prolongation is considered to be very low, in the event of prolongation of the QT/QTc interval > 500 msec or an increase of > 60 msec over baseline, study treatment should be discontinued and appropriate close (continuous) ECG monitoring in a hospital setting should be initiated until the opinion of a cardiologist is obtained.

6.6 Concomitant Treatment and Prohibited Medication

Patients are allowed to receive supportive care therapies (including cytokine, growth factors) concomitantly during the trial.

No anti-cancer therapy other than that given in this clinical trial; no immunotherapy; no hormonal cancer therapy; no radiation therapy (except palliative); and no experimental medications are permitted during the trial. All alternative therapies must first be approved by the Sponsor.

No poly (adenosine diphosphate [ADP]) ribose polymerase inhibitors are permitted until progression of disease (PD).

Concomitant use of paracetamol (acetaminophen) based compounds is allowed. However, caution should be taken when co-administrating APR-246 with high doses of paracetamol (i.e. 4 g/24 hrs). Use of paracetamol must be terminated if any liver function tests increase above normal ranges is detected.

Any disease progression that requires other specific antitumor therapy will be cause for discontinuation from the trial.

Antioxidants: Concomitant intake of acetylcysteine or other antioxidants might have a negative effect on the treatment efficacy and is therefore not recommended.

Anticoagulant therapy: Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Concurrent or procedural medications or therapy given to or taken by the patient will be recorded in the CRF along with the indication. All concomitant medications should be recorded for up to 30 days following the last protocol treatment. After this period, only relevant medication (e.g. medication in patients with treatment related AEs) will be recorded in the CRF.

Both generic and trade names may be recorded. However, the generic name is generally preferred because of its specificity, whereas trade names are preferred for combination products.

The potential interaction of APR-246 with other medicinal products has not been investigated.

6.7 Contraception

Female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and their male partners must use a highly effective method of contraception resulting in a low failure rate (i.e. less than 1% per year) during chemotherapy treatment and for at least six months thereafter. These methods of contraception according to the note for guidance on non-clinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, barrier methods with spermicide, true sexual abstinence when this is in line with the preferred and usual lifestyle of the patient and partner with vasectomy. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception. If using hormonal contraception this method must be supplemented with a barrier method, preferably male condom (female condom and male condom should not be used together).

7.0 STUDY PROCEDURES

7.1 Schedule of Study Procedures

Study evaluations are summarized in the Table 9 and Table 10 below and described in Sections 7.2 through 7.2.7.

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Table 9. Schedule of Study Evaluations in Arm A

	Pre-treatment [1]	Cycle 1					Cycle 2 and subsequent cycles						EoT[14]	FU[15]
Day		1	2	3	4	5	1	2	3	4	5	25-28		
Eligibility Criteria	X													
Registration/Randomization and Informed Consent	X													
Medical History	X	X*												
Quality of Life Questionnaires	X											X[10]	X	X[9]
Tumor Assessment[2]	X											X	X	X
Physical Exam/ECOG	X	X*					X						X	X[11]
Vital Signs	X	X	X	X	X		X	X	X	X				
Hematology/Coagulation	X	X*					X*						X	
Blood Chemistry	X	X*					X*						X	
Creatinine Clearance	X													
CA-125		X*					X*						X	X[8]
Urinalysis	X	X*					X*							
Serum Pregnancy Test (women of child bearing potential)	X													
LVEF[3]	X						X[3]							
ECG[4]	X												X	
Tumor Biopsy[5] (optional)	X			X										
Exploratory Biomarkers	X	X			X	X[13]	X[7]			X[7]	X[7,13]		X	X[8]
Administer APR-246		X	X	X	X		X	X	X	X				
Administer Chemotherapy					X					X				
Adverse Events and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival														X[12]
Pharmacokinetics[6]		X	X		X									

Examinations marked * need not be repeated if already performed within 3 days prior to Day 1.

1. Pre-treatment evaluations are to be performed within 28 days of Day 1 of Cycle 1.
2. A CT scan/MRI should be performed at pre-treatment (within 4 weeks prior to day 1 of study treatment) and at the end of cycle 2 (within 7 days prior to the start of cycle 3), and at the end of cycle 4 (within 7 days prior to the start of cycle 5), after the last cycle, 2 months (± 2 weeks) after the end of treatment (EoT) visit and every 3 months (± 2 weeks) thereafter, until the documented disease progression, as determined by the Investigator at each site and defined by RECIST v1.1. Confirmatory scans to be done at least 28 days after scan performed post last treatment cycle for all patients initially assessed as having a radiological response.
3. LVEF assessed by echocardiography between day 21 of cycle 2 and start of cycle 3, and day 21 of cycle 4 and start of cycle 5. LVEF is mandatory before each additional administration of PLD that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2. Additional echocardiograms can be conducted if clinically indicated per institutional practices.

4. ECG will be monitored as per the standard of care for PLD treatment.
5. One tumor biopsy to be performed within 4 weeks prior to day 1 APR-246 infusion and one tumor biopsy to be performed cycle 1, day 3, per laboratory manual (optional).
6. For sparse PK sampling schedule on Cycle 1, days 1, 2, and 4, please refer to Section 8.4.
7. Only Cycle 2 day 1, 4, 5 and Cycle 6, day 1.
8. Blood samples should be taken at each follow up visit until progression, as per laboratory manual.
9. To be performed the first 4 follow up visits only.
10. QoL to be performed at each radiological tumor assessment time point.
11. Physical examination only, excludes ECOG.
12. Patients to be followed until death. Survival after progression will be monitored (e.g. via telephone, via General Practitioner or via review of medical records) every 6 months. The start date of the first subsequent treatment will be collected and recorded.
13. 18-72h after the end of infusion of APR-246.
14. End of treatment (EoT) visit should take place 7 days after the completion of 6 cycles of chemotherapy (between day 28 and day 35 of cycle 6) or up to 30 ± 2 days after the last administration of APR-246 if treatment is stopped early for any reasons.
15. The first follow-up visit should commence 2 months (± 2 weeks) after the EoT visit. Subsequent follow-up visits should be performed every 3 months (± 2 weeks) until documented disease progression as defined by RECIST v1.1.

Table 10. Schedule of Study Evaluations in Arm B

	Pre-treatment [1]	Cycle 1				Cycle 2 and subsequent cycles					EoT[13]	FU[14]
Day		1	2	3	4	1	2	3	4	25-28		
Eligibility Criteria	X											
Registration/Randomization and Informed Consent	X											
Medical History	X	X*										
Quality of Life Questionnaires	X									X[9]	X	X[8]
Tumor Assessment[2]	X									X	X	X
Physical Exam/ECOG	X	X*				X					X	X[10]
Vital Signs	X	X				X						
Hematology/Coagulation	X	X*				X*					X	
Blood Chemistry	X	X*				X*					X	
Creatinine Clearance	X											
CA-125		X*				X*					X	X[7]
Urinalysis	X	X*				X*						
Serum Pregnancy Test (women of child bearing potential)	X											
LVEF[3]	X					X[3]						
ECG[4]	X										X	
Tumor Biopsy (optional)	X[5]											
Exploratory Biomarkers	X	X	X[12]			X[6]	X[6,12]				X	X[7]
Administer Chemotherapy		X				X						
Adverse Events and Concomitant Medication	X	X	X			X	X	X	X	X	X	
Survival												X[11]

Examinations marked with * need not be repeated if already performed within 3 days prior to Day 1.

1. Pre-treatment evaluations are to be performed within 28 days of Day 1 of Cycle 1.
2. For patients in Arm B: A CT scan/MRI should be performed at pre-treatment (within 4 weeks prior to day 1 of chemotherapy administration) and at the end of cycle 2 (within 7 days prior to the start of cycle 3), and at the end of cycle 4 (within 7 days prior to the start of cycle 5), after the last cycle, 2 months (± 2 weeks) after the EoT visit and every 3 months (± 2 weeks) thereafter, until the documented disease progression, as determined by the Investigator at each site and defined by RECIST v1.1. Confirmatory scans to be done at least 28 days after scan performed post last treatment cycle for all patients initially assessed as having a radiological response.
3. LVEF assessed by echocardiography between day 21 of cycle 2 and start of cycle 3, and day 21 of cycle 4 and start of cycle 5. LVEF is mandatory before each additional administration of PLD that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2. Additional echocardiograms can be conducted if clinically indicated per institutional practices.
4. ECG will be monitored as per the standard of care for PLD treatment.
5. One tumor biopsy to be performed within 4 weeks prior to day 1 chemotherapy administration (optional).

6. Only cycle 2 days 1 and 2, and cycle 6 day 1.
7. Blood samples should be taken at each follow up visit until progression, as per laboratory manual.
8. To be performed at the first 4 follow up visits only.
9. QoL to be performed at each radiological disease assessment time point.
10. Physical examination only, excludes ECOG.
11. Patients to be followed until death. Survival after progression will be monitored (e.g. via telephone, via General Practitioner or via review of medical records) every 6 months. The start date of the first subsequent treatment will be collected and recorded.
12. 18-72h after the end of infusion of chemotherapy.
13. EoT visit should take place 7 days after the completion of 6 cycles of chemotherapy (between day 28 and day 35 of cycle 6) or up to 30 ± 2 days after the last administration of APR-246 if treatment is stopped early for any reasons.
14. The first follow-up visit should commence 2 months (± 2 weeks) after the EoT visit. Subsequent follow-up visits should be performed every 3 months (± 2 weeks) until documented disease progression as defined by RECIST v1.1.

7.2 Detailed Study Evaluations for Arm A and B

The following sections provide details of the study evaluations to be conducted pre-treatment, during study and in follow-up. Please refer to Table 9 for Arm A and Table 10 for Arm B for a complete schedule assessments required.

7.2.1 Registration /Informed Consent Form

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all patient candidates and written informed consent will be obtained. Patients who choose to participate will have to consent to the biobanking program and will be asked to sign the mandatory section in the main study consent form related to biobank samples. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

7.2.2 Pre-treatment

All pre-treatment evaluations are to be performed within 28 days of day 1 unless otherwise noted. Please see Table 9 and Table 10 for treatment windows for individual evaluations.

- **Eligibility criteria**: Including archived tumor sample review for positive IHC staining for p53.
- **Medical history.**
- **Quality of Life Questionnaires**
- **Tumor assessment**: CT scan/MRI.
- **Physical examination**: Height, weight, body surface area, and description of external signs of cancer.
- **ECOG performance status**.
- **Vital signs**: Heart rate, blood pressure, respiratory rate and temperature.
- **Hematology**: Hemoglobin, hematocrit, MCV, platelet count, WBC and WBC differentials.
- **Coagulation**: INR and APTT, if patient is receiving warfarin assessments should be done weekly.
- **Blood chemistry**: Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin and lactic dehydrogenase [LDH], direct bilirubin and uric acid.
- **Creatinine clearance**: Calculated as per hospital practice.
- **Urinalysis**: Dipstick for protein, glucose, bilirubin and blood (perform microscopy if more than one positive dipstick test).
- **Serum pregnancy test**: For patients with reproductive potential.
- **LVEF**: Assessed by echocardiography within 4 weeks prior to Day 1. MUGA may be used

as an alternative.

- **ECG**: Standard 12-lead ECG.
- **Exploratory biomarkers:** Archive pathology samples and blood samples to be sent for p53 centralized analysis after registration. Refer to laboratory manual for detailed instructions.
- **Adverse events**: from the date the Informed Consent form is signed.
- **Concomitant medication.**

7.2.3 Randomization

- **Randomization**: Optimally performed prior to any biopsy. See Section 4.4 for procedure.

- **Tumor biopsy (optional)**: Arm A tumor biopsy to be performed within 28 days prior to cycle 1 day 1 APR-246 infusion. Arm B tumor biopsy to be performed within 28 days prior to cycle 1 chemotherapy administration.

7.2.4 All Cycles, Days 1 - 28

Day 1 examinations marked ***** do not need to be repeated if already performed within 3 days prior to day 1 cycle 1.

- **Medical history**: Only cycle 1*****.
- **QoL questionnaires:** To be completed at each radiological tumor assessment time point.
- **Tumor Assessments**: CT scan/MRI at the end of cycle 2 (within 7 days prior to the start of cycle 3) and at the end of cycle 4 (within 7 days prior to the start of cycle 5).
- **Physical examination**: Day 1*. Height, weight, body surface area, and description of external signs of cancer.
- **ECOG performance status**: Day 1.
- **Vital signs**: Arm A on Days 1, 2, 3 and 4. Arm B only on Day 1. Heart rate, blood pressure, respiratory rate and temperature.
- **Hematology**: Day 1* (repeat to follow up on AEs as appropriate). Hemoglobin, hematocrit, MCV, platelet count, WBC and WBC differentials.
- **Coagulation**: Day 1*. INR and APTT, if patient is receiving warfarin assessments should be done weekly.
- **Blood chemistry**: Day 1*. (repeat to follow up on AEs as appropriate). Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, lactic dehydrogenase [LDH], direct bilirubin and uric acid.
- **CA-125**: Day 1*
- **Urinalysis**: Day 1*. Dipstick for protein, glucose, bilirubin and blood (perform microscopy if more than one positive dipstick test).
- **LVEF**: Assessed by echocardiography between day 21 of cycle 2 and start of cycle 3, and day 21 of cycle 4 and start of cycle 5. LVEF is mandatory before each additional

administration of PLD that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2. Additional echocardiograms can be conducted if clinically indicated per institutional practices.

- **Tumor biopsy (optional)**: Arm A only. One tumor biopsy to be performed optimally at the end of APR-246 infusion on day 3 of the first cycle, however a biopsy obtained at the end of the APR-246 infusion on day 2 is acceptable. Refer to laboratory manual for detailed instructions.
- **Pharmacokinetics**: Arm A only. On Cycle 1, days 1, 2, and 4; please refer to Section 8.4 for PK sampling time points.
- **Exploratory biomarkers**: Arm A blood samples. Cycle 1 on days 1, 4 and 5. Cycle 2 on days 1, 4 and 5. Cycle 6 on day 1. Arm B blood samples. Cycle 1 and 2 on days 1 and 2. Cycle 6 on day 1. Refer to laboratory manual for detailed instructions.
- **APR-246 administration**: Arm A only on days 1, 2, 3 and 4.
- **Chemotherapy administration (Carboplatin and PLD)**: Arm A on day 4. Arm B on day 1.
- **Adverse Events**: All adverse events since the last visit should be recorded. Even though pre-medicated, patients should be closely monitored.
- **Concomitant medications.**

7.2.5 End of Treatment Visit

This visit should take place 7 days after the completion of 6 cycles of chemotherapy (between day 28 and day 35 of cycle 6) or up to 30 ± 2 days after the last administration of APR-246 if treatment is stopped early for any reasons.

- **Physical examination***: Height, weight, body surface area, and description of external signs of cancer.
- **QoL questionnaires**
- **Tumor Assessment**: CT scan/MRI. If the patient has stopped APR-246 treatment prior to completion of 6 cycles, tumor assessment should be performed at end of treatment visit if not done at the last cycle.
- **ECOG performance status**.
- **Hematology**: Hemoglobin, hematocrit, MCV, platelet count, WBC and WBC differentials.
- **Coagulation**: INR and APTT, if patient is receiving warfarin assessments should be done weekly.
- **Blood chemistry**: Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin and lactic dehydrogenase [LDH], direct bilirubin and uric acid.
- **CA-125**.
- **ECG**: Standard 12-lead ECG.
- **Exploratory biomarkers**: Blood Sample. Refer to laboratory manual for detailed instructions.

7.2.6 Follow-up Visits

The first follow-up visit should commence 2 months (± 2 weeks) after the end of treatment visit. Subsequent follow-up visits should be performed every 3 months (± 2 weeks) until documented disease progression, as defined by RECIST v1.1.

- **Physical examination**: Description of external signs of cancer until progression.
- **QoL questionnaires (first four follow up visits only)**
- **CA-125:** Disease will be followed by GCIG Criteria until progressive disease and then confirmed by CT scan/MRI.
- **Exploratory biomarkers:** Blood samples taken at each visit until progression. Refer to laboratory manual for detailed instructions.
- **Tumor Assessment (by CT/MRI):** Tumor assessments by a CT scan/MRI will be performed 2 months (± 2 weeks) after the end of treatment visit and every 3 months (± 2 weeks) thereafter, until the documented disease progression, as defined by RECIST v1.1.

All patients will be followed until initial progression. Information on survival and subsequent therapies will be collected.

7.2.7 After Progression

Survival after progression will be monitored every 6 months. This can be done remotely (e.g. via telephone, via General Practitioner or via review of medical records). The start date of the first subsequent treatment will be collected and recorded.

7.3 Adverse Events

7.3.1 Definition of Adverse Events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an AE as far as the deterioration can be anticipated (see Section 7.3.3.8).

The term adverse event is used generally to include any AE whether serious or non-serious.

7.3.2 Definitions of Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening (i.e., the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization, unless the hospitalization is for:
    - Routine treatment or monitoring of the disease under study, including hospitalization due to trial related procedures (e.g. APR-246 administration) not associated with any deterioration of the patient's status;
    - Elective treatment (planned before signing Informed Consent) for a pre-existing condition that is unrelated to the disease under study and has not worsened since signing Informed Consent;
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions for an SAE;
    - Social reasons, respite care in the absence of a medical condition.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event (may not be immediately life-threatening or result in death or hospitalization) that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Section 7.3.3.10 below and also Appendix III of this Clinical Study Protocol.

7.3.3 Recording of Adverse Events

7.3.3.1 Time Period for Collection of Adverse Events

AEs will be collected throughout the study, from informed consent until 30 days after the last administration of study treatment.

SAEs occurring in this period should be reported to the Theradex® Safety Desk in the usual manner (see Section 7.3.4).

Events which are unequivocally due to a worsening of a patient's condition, attributable to the disease for which the investigational product is being studied, which occur after informed consent but before the patient is registered, should not be reported as an AE or SAE during the study.

7.3.3.2 Follow-up of Unresolved Adverse Events

All AEs should be followed until they are resolved or until the end of treatment (EoT) visit, whichever comes first. All AEs that are still ongoing after the EoT visit, should be followed on a regular basis, according to the Investigator's clinical judgment, until the event has resolved or until the Investigator assesses it as chronic and all queries have been resolved. After the EoT visit, AEs that are unrelated to APR-246 (serious or non-serious) or related but not serious, do not require further recording in the eCRF. For related SAEs that have been resolved, the event resolved date and the outcome of resolved or resolved with sequelae, as appropriate, should be recorded on the eCRF and the SAE Report Form. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an Investigator learns of any SAEs, including death, at any time following 30 days after the last administration of study treatment and he/she considers there is a reasonable possibility that the SAE is related to the study treatment, the Investigator should notify Theradex® Safety Desk.

7.3.3.3 Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date the AE started and stopped
- CTCAE version 4.0 grade
- Whether the AE is serious or not and the reason(s) it is serious
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to study treatment
- Outcome

For SAEs other variables will be collected including treatment given for the event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The grading scales found in the current National Cancer Institute CTCAE version 4.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

7.3.3.4 Causality Collection

The Investigator will assess causal relationship between investigational product 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 other medication and study procedure(s).

A guide to the interpretation of the causality question is found in Appendix III of this Clinical Study Protocol.

7.3.3.5 Adverse Events based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open-ended and non-leading verbal questioning from the study personnel (e.g., "*How are you feeling?" "Have you had any health problems since the previous visit/you were last asked?"*), or revealed by observation will be collected and recorded in the eCRF. Where possible a diagnosis should be recorded, rather than recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.3.3.6 Adverse Events based on Examinations and Tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the Clinical Study Report. Deterioration as compared to pre-treatment in these parameters will therefore only be reported as AEs if they fulfill any of the criteria for a SAE or are the reason for modifying the study treatment unless clearly due to progression of disease under study (see Section 7.3.3.8).

If deterioration in a laboratory value, vital sign, ECG, or other safety assessment is associated with clinical events, the clinical event will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting Investigator will use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical events, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the pre-treatment assessment will be reported as an AE.

7.3.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT elevations in liver biochemistry that may require further evaluation

should be reported as SAEs. Please refer to Appendix IV for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

7.3.3.8 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

7.3.3.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

7.3.3.10 Handling of Deaths

All deaths that occur during the study, or within the 30-day follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the Theradex® Safety Desk as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to the Theradex® Safety Desk within the usual timeframes.

7.3.4 Reporting of Serious Adverse Events

All SAEs have to be reported to the Theradex® Safety Desk, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study (from signing of informed consent up to 30 days after last dose), then Investigators or other site personnel must inform the Theradex® Safety Desk

immediately, or **no later than 24 hours** of when he or she becomes aware of it.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform the Theradex® Safety Desk of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

All SAEs require that a Serious Adverse Event Report Form be completed and forwarded either via fax or as a PDF via email to the Theradex® Safety Desk at the fax number or email listed below within 24 hours of becoming aware of the event. The fax and telephone numbers listed below may be used during both business and non-business hours. During non-business hours a recorded message will provide the caller with the contact information for the on-call monitor.

EU and US sites will report SAEs to:	Theradex® (Europe) Ltd. Safety Desk ***REDACTED***

7.4 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to the Theradex® Safety Desk using the appropriate forms.

7.4.1 Maternal Exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 30 days after discontinuing investigational product, then Investigators or other site personnel must inform the Theradex® Safety Desk immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

8.0 EFFICACY ASSESSMENTS

Patients with measurable disease will be assessed by standard criteria.

For patients in Arm A or Arm B: A CT scan/MRI should be performed at pre-treatment (within 4 weeks prior to day 1 of study treatment) and at the end of cycle 2 (within 7 days prior to the start of cycle 3), and at the end of cycle 4 (within 7 days prior to the start of cycle 5), and after the last cycle. At subsequent follow-up visits, tumor assessments by CT scan/MRI will be performed 2 months (± 2 weeks) after the end of treatment visit and every 3 months (± 2 weeks) thereafter, until the documented disease progression, as determined by the Investigator at each site and defined by RECIST v1.1.

Central reading for all scans will be performed during the study. After CT/MRI acquisition, the exam will be transferred for central reading by two expert readers (see Radiology Manual for further details). The central reader will visualize the image in order to evaluate the clinical response based on RECIST v1.1 criteria. The central review will be performed in batches throughout the study. Treatment decisions should be based upon results of the local review.

8.1 Definitions

Response and progression will be evaluated in this study using the international criteria (version 1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [14] and CA-125 definitions for response and progression agreed by the Gynecological Cancer Intergroup (GCIG) [12].

Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.1.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension [longest diameter (LD) in the plane of measurement to be recorded] with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

8.1.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or MRI.

Bone lesions, cystic lesions and lesions previously treated with local therapy must be considered as follows:

8.1.2.1 Bone Lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (i.e., CT scan or MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

8.1.2.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

8.1.2.3 Lesions with Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

8.1.3 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at pre-treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging

techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the pre-treatment sum diameters. The pre-treatment sum diameters will be used as reference by which to characterize the objective tumor response.

8.1.4 Lymph Node Assessment

For lymph nodes, measurements should be made of the short axis, which is defined as perpendicular to the LD of node assessed in the plane of measurement:

- Target lesion if short axis ≥ 15 mm
- Non-target lesion if short axis is ≥ 10 but < 15 mm
- Normal if short axis < 10 mm

For pre-treatment, add the actual short axis measurement to the sum of LD of non-nodal lesions.

8.1.5 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at pre-treatment. Measurements of these lesions are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

8.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All pre-treatment evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
(Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the Sponsor/Investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.)

The same method of assessment and the same technique (CT and/or MRI) should be used to characterize each identified and reported lesion at pre-treatment and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest x-ray. Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Conventional CT scan and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is acceptable in certain situations (e.g., for body scans).

Ultrasound (US). US should not be used to measure tumor lesions. US examinations cannot be reproduced in their entirety for independent review at a later date because they are operator dependent. If new lesions are identified by US, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

8.3 Response Criteria

8.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the pre-treatment sum diameters.

Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the pre-treatment sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression.)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.3.1.1 Assessment of Target Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the pre-treatment exam), even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

8.3.1.2 Target Lesions that Become "Too Small to Measure"

All lesions (nodal and non-nodal) recorded at pre-treatment should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

8.3.1.3 Lesions that Split or Coalesce on Treatment

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter should be the maximal longest diameter for the 'coalesced lesion.'

8.3.2 Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation. (*Note:* the appearance of one or more new lesions is also considered progression.)

8.3.2.1 New Lesions

The finding of a new lesion should be unequivocal (i.e., not attributed to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor, such as a 'new' healing bone lesion). A lesion identified on a follow-up study in an anatomical location that was not scanned at pre-treatment is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm this is definitely a new lesion, then progression should be declared using the date of the initial scan.

8.3.2.2 Evaluation of Best Overall Response by RECIST v1.1

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 11 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at pre-treatment. When patients have non-measurable disease, Table 12 should be used.

Table 11. Time Point Response: Patients with Target (+/- non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=complete response, PR=partial response, SD=stable disease PD=progressive disease, NE=inevaluable			

Table 12. Time Point Response: Patients with Non-target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR / non-PD	No	Non-CR / non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response; PD=progressive disease; NE=inevaluable * Non-CR/non-PD is preferred over SD for non-target disease		

Best response determination for studies where confirmation of CR or PR is required: Complete or partial responses may be claimed only if the criteria for each are confirmed by a repeat assessment at least 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 13.

Table 13. Best Overall Response when Confirmation of CR and PR is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=inevaluable

* If CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to pre-treatment, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in the fact patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

8.3.2.3 Evaluation of Best Overall Response in Patients with Initial Measurable Disease and who are also Evaluable by CA-125

For patients who are measurable by one or both of the criteria and who may have events at different time points evaluation should be determined according to Table 14. In patients who have measurable disease by both criteria, the date of response will be the date of the earlier of the 2 events if this approach to combined response reporting is to be used.

In the combined assessment of CA-125 and RECIST v1.1 response, the following algorithm applies when determining the best overall response:

- If patients have progressive disease (PD) according to RECIST v1.1 within 28 days of CA-125 response, they are classified as having PD.
- If the PD according to RECIST v1.1 is longer than 28 days before or after the CA-125 response, they are classified as having partial response.
- Patients whose best response according to RECIST v1.1 is stable disease but who have a CA-125 response are classified as CA-125 responders.

Table 14. Best Overall Response in Patients with Initial Measurable Disease and Evaluable by CA-125, Combining Both Criteria

Target Lesion *	Non Target *	New Lesion	CA-125	Overall Best Response	
CR	CR	No	Normal	CR	Best RECIST v1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days
CR	Non CR Non PD	No	Not PD	PR	
CR	CR	No	PR 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	

*According to RECIST v1.1 criteria
‡Patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST v1.1 are considered a PR, according to best response, but PD if the RECIST v1.1 PD is within 28 days of CA-125 response.
§ For SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6-8 weeks
NE Not evaluated; NAE not all evaluated.

8.3.3 Confirmatory Measurement/Duration of Response

8.3.3.1 Confirmation According to RECIST v1.1

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6-8 weeks.

8.3.3.2 Definition of Response According to CA-125

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

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

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies [unless the assay used has been shown not to be influenced by human antimouse antibody [12]] or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (e.g., surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

8.3.3.3 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.3.3.4 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.3.4 Progression-free Survival

Progression-free survival (PFS) is defined as the time from randomization to the time of disease progression or relapse (according to RECIST v1.1. PFS by CA-125 criteria is a separate secondary endpoint) or death, or to the date of last tumor assessment without any such event (censored observation) and includes any of the following

- Occurrence (clinically or imaging signs) of any new lesion
- Increase in measurable and/or non-measurable tumor as defined by the RECIST v1.1 criteria
- CA-125 elevation as defined by the GCIG criteria

- Deterioration in general health attributable to the disease.

8.3.4.1 Definition of Progression on Therapy and Recurrence after Therapy According to CA-125

Progression (PD) is conventionally defined according to RECIST v1.1 but can also be based on serum CA-125 (defined below). However, in assigning the date of progression, PD by objective change in tumor size should always take precedence over CA-125 should it occur first. If measurable disease is reducing in size during treatment but the CA-125 results suggest progression (as defined below), the patient should continue to receive protocol treatment. If measurable disease is stable but CA-125 indicates confirmed progression over at least 4 weeks, treatment should be discussed with the Sponsor. If patients are having routine CA-125 measurements as part of follow-up, the date of progression is likely to be several months earlier than symptoms or signs of progression develop [15]. Therefore, when categorizing patients according to time to progression, it is necessary to specify how the date of progression was defined (CA-125 alone, CA-125 and symptoms, and RECIST v1.1).

8.3.4.2 Evaluation of Progression According to CA-125

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria and Table 15:

A. Patients with elevated CA-125 pretreatment and normalization 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 or
B. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart or
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.

CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura (e.g., paracentesis) during the previous 28 days.

A patient may be declared to have PD on the basis of either the objective RECIST v1.1 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.

For the purposes of study objectives and analysis of the study end-points, PD will declared based on objective RECIST v1.1 data only. PFS by CA-125 criteria is a separate secondary end-point.

Table 15. Definition of Progression after First-line Therapy in Ovarian Cancer as Proposed by the GCIG

GCIG Subcategorized group	RECIST Measurable/non-measurable disease		CA-125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST v1.1 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 two occasions* Date of PD: first date of the CA-125 elevation to ≥ 2x ULRR
B	As for A		CA-125 ≥ 2x nadir value on two occasions* Date of PD: first date of the CA-125 elevation to ≥ 2x nadir value
C	As for A		As for A
CA-125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days should not be taken into account. *Repeat CA-125 any time but normally not less than 1 week after the first elevated CA-125 level.			

8.4 Pharmacokinetics

Sparse blood sampling for APR-246 pharmacokinetic (PK) measurements will be performed from all patients in Arm A at days 1, 2 and 4 in Cycle 1 (Table 16).

Please refer to the laboratory manual for detail instructions on processing of the pharmacokinetic samples.

Table 16: Sparse PK Blood Sampling Time Points for APR-246 in Cycle 1 (Arm A)

Day 1	Before infusion	0-2 h prior APR-246 infusion (nominal time point 0 h)
	At end of rapid phase	45 min (at the end of first part of infusion) (nominal time point 0.75 h)
	At end of infusion	± 5 min relative to the end of infusion (nominal time point 6 h)
	After infusion	30-60 min AFTER infusion (nominal time point 7 h)
Day 2	Before infusion	0-2 h prior APR-246 infusion (nominal time point 24 h)
Day 4	Before infusion	0-2 h prior APR-246 infusion (nominal time point 0 h)
	At end of rapid phase	45 min (at the end of first part of infusion) (nominal time point 0.75 h)
	At end of infusion	± 5 min relative to the end of infusion (nominal time point 6 h)
	After infusion	30-60 min AFTER infusion (nominal time point 7 h)

8.5 Pharmacodynamics

8.5.1 Optional Tumor Biopsy

Archived tumor tissue (FFPE sections) from all patients will be reviewed by a gynecological pathologist to confirm the diagnosis of high grade serous ovarian cancer, and positive IHC staining for p53. In addition, these samples will be used to determine p53 status by a central laboratory.

Additional analysis may include biomarkers and evaluation of tumor cell DNA.

Optional paired tumor biopsies will be collected in Arm A: one prior to treatment and the other during treatment (optimally within the last 30 minutes of the APR-246 infusion on day 3 of the first cycle, however a biopsy obtained at the end of the APR-246 infusion on day 2 is acceptable). For Arm B, one tumor biopsy to be performed prior to chemotherapy.

Two tumor cores will be taken at each biopsy, one will be flash frozen and one will be formalin fixed.

The choice of the tumor lesion is at the Investigator's discretion. If either tumor biopsy fails, the patient can still be included in the trial. The reasons for failure to obtain a biopsy must be recorded in the eCRF. If the pre-treatment tumor biopsy is not obtained, no further tumor biopsies will be attempted.

Any lesion that is used for biopsy purposes should be recorded as a non-target lesion only.

The following assessments may be performed by Aprea Therapeutics AB or a central laboratory appointed by Aprea Therapeutics AB (please refer to Laboratory Manual).

- Immunohistochemistry for tumor cellularity and p53 protein staining and other IHC markers (i.e. BRCA1, ER stress markers)
- RNA/DNA extraction for microarray tumor gene expression profiling
- Proteomics - Lysates for reverse phase proteomics

Specimens may be stored for future evaluation of APR-246 in target tissue.

The quality and quantity of the biopsy will determine which analyses are to be performed. The mutational analyses will be done in batches and the results will not be reported to the trial site during the treatment period.

8.6 Exploratory Biomarker Research

Serum, plasma, whole blood and tumor samples will be collected from all patients and stored for retrospective exploratory analyses. These analyses may include (but are not necessarily limited to):

- Predictive markers of efficacy, tolerability and clinical pharmacology
- Biomarkers of acquired or innate resistance to APR-246
- Circulating free tumor DNA

The results of the exploratory biomarker research will be reported separately and will not be part of the Clinical Study Report.

A blood sample will be taken pre-treatment for collection of germ line DNA in order to allow comparison of germ-line and tumor cell DNA sequence.

The results of exploratory biomarker research may be pooled with data from other studies with APR-246 to generate hypotheses to be tested in future studies.

8.7 Biological Sample Handling

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual. Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way exploratory biomarker and genetic data may be correlated with clinical data. Samples will be destroyed in the case of withdrawal of consent and regulatory audit enabled. Where genetic analysis will be undertaken the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of sample, the DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the Aprea Therapeutics AB's designated contract laboratory. No personal details identifying the individual will be available to any person (Aprea Therapeutics AB or contract laboratory staff) working with the DNA. The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analyzed.

8.8 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their lifecycle. The Principal Investigator at each center keeps full traceability of collected biological samples from the patients

while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival. The Principal Investigator will also ensure that access to the samples while in storage at the study center will be limited only to those people for whom access is required. The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival. Aprea Therapeutics AB keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers. Samples retained for further use will be registered in the Aprea Therapeutics AB biobank system during the entire life cycle. Samples will be stored for up to 15 years.

8.9 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, Aprea Therapeutics AB is not obliged to destroy the results of this research. As collection of the genetic blood sample is a voluntary part of the study then the patient may continue in the study.

9.0 STATISTICS

9.1 Primary Endpoint

The primary endpoint is progression-free survival (PFS) based on BICR and is defined as the number of days from the date of randomization to the date of objective disease progression or relapse (according to RECIST v1.1 only) or death due to any cause, whichever occurs first. If neither event occurs, PFS will be censored at the date of the last evaluable tumor assessment. Symptomatic deterioration is not objective disease progression.

9.2 Secondary Endpoints

Secondary endpoints include:

- Best overall response and overall response rate (according to RECIST v1.1 and GCIG Criteria)
- Duration of response (complete or partial response)
- PFS by assessment of CA-125 (according to GCIG Criteria)
- Overall survival
- Safety profile based on AEs and laboratory assessments
- Evaluation of biomarkers and tumor activity based on CA-125
- Quality of Life assessment using EORTC Ovarian (QLQ-30 and QLQ-OV28) and the Functional Assessment of Cancer Therapy-Ovarian (FACT-O)

9.3 Sample Size

Adaptive Sample Size

The trial will enroll up to a maximum of 400 patients, randomized between two arms (treatment and control).

This phase II study has a flexible sample size. The purpose is to use a smaller sample size with very small or very large observed effect sizes, and a larger sample size where observed effect sizes are promising but more data are needed. For small observed effect sizes (with typically smaller sample sizes), the study results will have traditional phase II interpretations. However, for moderate/large observed effect sizes (with potentially larger sample sizes), the design is intended to provide sufficient evidence to justify regulatory conditional approval.

9.4 Analysis Populations

All randomized subjects will be analyzed according to the group in which they were randomized.

Intent-to-Treat (ITT): All randomized patients will be included in the intent-to-treat (ITT) population. The ITT population will serve as the primary analysis population for efficacy.

Safety Evaluable Population: All randomized patients who received any amount of study medication (APR-246, carboplatin, or PLD) will be considered evaluable for safety, regardless of the duration of treatment. This population will be used to summarize all safety parameters.
Efficacy Evaluable Population: All randomized patients with pre-treatment measurable disease by RECIST v1.1 who have at least one radiographic assessment after pre-treatment or discontinue study medication early due to disease progression and have a TP53 mutation will be considered evaluable for efficacy. The efficacy-evaluable population will be the secondary analysis population for efficacy.

9.5 Statistical Methods

All demographic data and disease-related characteristics will be summarized using descriptive statistics (count and percent, mean, median, standard deviation, minimum, maximum), separately for phase Ib and phase II parts of the study.

9.5.1 Safety Analysis

Safety data will be summarized for the safety evaluable population. These data will include adverse events and laboratory parameters. Adverse event terms will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®, version 16.0 or higher). Adverse events will be summarized by body system, preferred term, severity, and relationship to treatment. Serious adverse events, deaths, and AEs leading to early discontinuation of study drug will be summarized. Laboratory parameters will be summarized by maximum NCI-CTCAE-4.0 severity grade and also by change from pre-treatment to scheduled time points using descriptive statistics. Laboratory parameter listings will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range.

Data summaries will include only treatment-emergent adverse events (TEAEs), defined as events occurring on or after Day 1 Cycle 1 up to and including 30 days after last dose.

9.5.2 Phase II Analysis

9.5.2.1 Primary analysis

At the final analysis (which occurs after 12 months of follow-up after the last patient is enrolled), a one-sided p-value is calculated for a stratified logrank test comparing treatment versus control. This corresponds to a formal test of the null hypothesis that the survival (event free) distribution of the treatment group is less than or equal to the survival distribution of the control group, i.e.

$$H_0: S_T(t) \leq S_C(t)$$
$$H_a: S_T(t) > S_C(t)$$

where $S_T(t)$ and $S_C(t)$ are the survival distributions for the treatment and control groups, respectively, and $t > 0$ denotes observation time. The stratification factors for the test include

previous PFI (6-12, 12-24 months), BRCA status (known positive versus other) and prior lines of platinum-based treatment (1,2). The treatment will be considered superior to control if the corresponding one-sided p-value is less than or equal to 0.023. If the p-value is greater than 0.023 but less than 0.10, there may be sufficient promise to conduct another trial. The significance level of 0.023 is selected to control the overall Type I error of the adaptive design to be less than 0.025, as shown via simulation.

9.5.2.2 Secondary analysis

Tumor response data will be summarized at each tumor assessment cycle using the following response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE). Best overall response for a patient is the best response recorded from the start of the treatment until disease progression or death. Best overall response will be summarized as the number (%) of patients in each category of response (CR, PR, SD, PD, and NE). PR and CR must be confirmed by a repeat assessment at least 28 days after the criteria are first met for the response to be considered a PR or CR.

The overall response rate is defined as the percentage of patients with a confirmed response of CR or PR in a given population.

The duration of response (confirmed CR or PR) is defined as the number of days from the date of initial response (not the confirmation date) to the date of objective disease progression or death due to any cause, whichever occurs first. If neither event occurs, duration of response will be censored at the date of the last evaluable tumor assessment. Symptomatic deterioration is not objective disease progression.

Overall survival (OS) is defined as the number of days from the date of randomization to the date of death. In the event of no death, overall survival will be censored at the last known alive date.

PFS by assessment of CA-125 will be analyzed. CA-125 progression is defined according to the Gynecologic Cancer InterGroup (GCIG) criteria. The relationship between CA-125 progression and radiological disease progression will be evaluated.

PFS, OS and duration of response will be analyzed using Kaplan-Meier methodology. Kaplan Meier curves will be plotted. Median survival and duration times will be estimated and their 95% confidence intervals based on Brookmeyer-Crowley methodology will be calculated. In addition, hazard ratios and 95% confidence intervals will be provided. For the overall response rate and categorical response rates, 95% confidence intervals will be calculated based on Clopper-Pearson methodology.

9.5.3 Pharmacokinetic Analysis

APR-246 concentrations will be determined by a validated HPLC tandem mass spectrometry

(LC/MS/MS) method and calculated PK parameters (Cl, Vss, C_{max}, AUC_{0-24}, $AUC_{0-\infty}$ and $t_{1/2}$) of APR-246 will be determined.

Individual and mean profiles of APR-246 concentrations will be presented graphically. Protocol-specified blood sampling times will be used in the graphical presentation.

No formal statistical analysis beyond descriptive statistics is planned. For each PK parameter, individual and mean data and summary statistics (including number of patients, arithmetic mean, geometric mean, SD, CV, median, Min and Max) will be presented.

9.6 Randomization/Stratification

In Phase II, patients will be centrally randomized in a 1:1 ratio to receive the carboplatin/PLD chemotherapy regimen with or without APR-246. Permuted block randomization will be used to randomize patients to study treatment. Study treatment will not be blinded.
The stratification factors to be used are:

- Platinum-free interval after previous platinum based regimen. >6-12 months vs. >12 to <24 months
- Prior Lines of Platinum Treatment. One line vs. two lines
- BRCA status. Known positive vs. Other

9.7 Statistical Modeling for Interim Analyses

Although the final analysis for the primary endpoint is a frequentist (stratified logrank) test, the model underlying the adaptive sample size selection is Bayesian in nature. As shown via simulation in the Appendix V , the design has control of Type I error rate.

9.7.1 Control Hazard Model

Let T_i be the progression event time (in months) for the primary endpoint for the *i*th patient, where an event represents a negative outcome for the patient. We model the event times for the control arm as piecewise exponential:

$$T \sim PE(\mathbf{\Lambda}),$$

where $\mathbf{\Lambda} = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ represents the set of baseline hazard rates (events per month) within each segment. The hazard is assumed to be constant within each segment, s, and modeled with prior

$$\lambda_s \sim \text{Gamma}(a_s, b_s),$$

where the gamma distribution has the following density function:

$$p(\lambda_s) = {b_s}^{a_s} \lambda_s^{a_s - 1} \exp(-b_s \lambda_s)/\Gamma(a_s).$$

The 4 segments of the model are defined in Table 17, along with the parameters of the non-informative prior distributions.

Table 17. Prior Parameters for the Control Hazard Model

Segment (s)	Interval(months)	a_s	b_s
1	0 - 6	1	1
2	6 - 12	1	1
3	12 - 18	1	1
4	18 - ∞	1	1

9.7.2 Model

The event times for the treatment group is also modeled as piecewise exponential, with hazard rates

$$h_s = \lambda_s \exp(\theta),$$

where θ is the log hazard ratio for treatment relative to control. By convention, hazard ratios less than one indicate treatment benefit. The log hazard ratio has the non-informative prior

$$\theta \sim N(0, 0.5^2),$$

and is assumed to be constant over time.

9.7.3 Quantities of Interest

9.7.3.1 Probability Superior to Control by the Target HR

Let the event hazard ratio for treatment versus control be denoted by $\text{HR} = \exp(\theta)$. At each interim analysis, we calculate the probability of being superior to control by assessing the posterior distribution of the hazard ratio relative to a targeted 0.8:

$$\Pr(HR < 0.8).$$

9.7.3.2 Predictive Probability of Success

At each interim analysis, we also calculate the predictive probability of success (PPoS) if accrual is halted at the current sample size and all patients are followed for a minimum of 12 months. For each iteration in the MCMC algorithm after burn-in, event times are imputed for each patient without an observed event among patients current enrolled, creating a single imputed data set for each MCMC iteration. A stratified logrank test is performed on each imputed data set, and PPoS is equal to the proportion of imputed trials with a one-sided p-value less than 0.023.

Although not currently included in the simulations, PPoS will also use longitudinal modeling of CA-125 to better inform the predictive probability calculation. Neither the CA-125 data nor the longitudinal model will be included in the final analysis; rather the data are used to better inform the

decision of stopping accrual for predicted success.

9.8 Adaptive Sample Size

The design uses adaptive sample size selection. This section will describe the allocation and decision rules.

9.8.1 Timing of Interim Analyses

Interim analyses will occur when 150, 200, 250, 300, and 350 patients are enrolled.

9.8.2 Allocation

The trial will enroll up to a maximum of 400 patients, with randomization to treatment and control in a fixed 1:1 ratio. Stratified randomization will be used. The stratification factors are prior lines of platinum-based treatment (1,2), platinum free interval (6-12, 12-24 months) and BRCA status (known positive versus other).

9.8.3 Criteria for Stopping Accrual

9.8.3.1 Stopping for predicted success

At each interim analysis beginning at 200 patients enrolled, the trial may stop enrollment for expected success if

$$\text{PPoS} > S_n$$

where S_n = 0.95 for each interim. If a success stopping rule is met, then a final analysis will be conducted 12 months after the last patient is enrolled. Additionally, data will remain blinded and the Sponsor will be informed by the DSMB that the study has reached a stopping boundary for predicted success. The trial will not stop for predicted success unless at least 200 patients are enrolled, per safety concerns. Hence, the first interim at 150 patients will only stop for a small observed effect.

9.8.3.2 Stopping for Small Observed Effect

At each interim analysis beginning at 150 patients enrolled, the trial may stop enrollment early for a small observed effect size if

$$\Pr(HR < 0.8) < F_n$$

where F_n = 0.30 for each interim. If this stopping rule is met, the Sponsor will be informed by the DSMB that the study has reached a stopping boundary for a small observed effect. The Sponsor may then choose to unblind data and release results prior to 12 months after the last patient is enrolled. If

data are unblinded and results are released, regulatory approval will not be sought and results may be used for the planning of future trials. Otherwise, the Sponsor may choose to continue to follow currently enrolled patients in a blinded manner until 12 months after the last patient is enrolled.

9.8.3.3 Stopping Boundaries

The stopping boundaries for the interim analyses are provided in Table 18.

Table 18. Stopping Boundaries for Success and Small Effect Size

Interim N	F_n	S_n
150	0.30	-
200	0.30	0.95
250	0.30	0.95
300	0.30	0.95
350	0.30	0.95

9.8.4 Operating Characteristics

Complete operating characteristics (including power and Type I error) are provided in the Statistical Appendix (See Appendix V) for a variety of scenarios. In general the design has about 0.70 power for detecting a hazard ratio of 0.70 or smaller with one-sided Type I error less than 0.025.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Monitoring of the Study and Regulatory Compliance

The project manager, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, and fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit the case report forms (CRFs) will be reviewed. Other pertinent study materials will also be reviewed with the Investigator's research staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine CRFs and individual patient's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All CRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2 Curricula Vitae of Investigators

All Principal Investigators and Sub-investigators will be required to provide a current signed and dated curriculum vitae and evidence of GCP training to Theradex®.

10.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative (Theradex®). Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial (e.g. change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10.4 Publication Policy

This is a collaborative EUTROC study. The first publication will include all patients. Centers recruiting 10 evaluable patients will be entitled to nominate one co-author. The highest recruiting center would be entitled to be the first author on the first publication of the phase 2 study. However, the Chief Investigator would be the senior author. Contribution to sample collection and analysis for the translational components of the study will be assessed on a case by case basis. The Investigator agrees to inform the Sponsor of any other publication or presentations on the study. All manuscripts, abstracts or presentations (in outline form with copies of slides if available) will be submitted to the Sponsor and Theradex® at least 30 days prior to the submission of the data for publication in order for the Sponsor to protect proprietary information. The Sponsor will review the submitted material within a reasonable period of time and will not unreasonably withhold publication permission.

11.0 ETHICAL CONSIDERATIONS

11.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated prior to any study-specific procedures being performed. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

In cases where minors or incapacitated patients are to be included, two sets of information sheets might be needed according to national regulations (not applicable for the PiSARRO). In addition to the information given to the patient's parent or legal representative, the patient should be given information according to his/her capacity to understand. This information should include, where appropriate, a statement that the patient's decision not to participate or to withdraw from a trial will be respected, even if consent is given by the parent/legal representative.

In all instances the Principal Investigator or an appropriately qualified delegee should consent the patient to the study. The patient should be given adequate time to read the information provided and consider whether she wants to participate in the study.

Only adult women who are mentally competent will be in enrolled and treated in this study.

11.2 Institutional Review Board/Independent Ethics Committee/Regulatory

The study will not be initiated without approval of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and compliance with all administrative requirements of the governing body of the institution as well as the national Competent Authority (CA) in each country. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC/CA in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC/CA will be kept informed by the Investigator, Theradex® or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected adverse events.

11.3 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers; patients should

not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the case report forms and to audit the data collection process. Regulatory agencies such as the US Food and Drug Administration (FDA) and the UK Medicine and Healthcare Products Regulatory Agency (MHRA) may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Data to be Recorded Directly in the Case Report Form

Not applicable.

12.2 Recording of Data

Data collected during the study will be recorded in the patient's electronic Case Report Form (eCRF) by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the eCRF in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRF.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data.

12.3 Study Records

European laws require that the Investigator maintain all study records (excluding the patient's medical files, see below):

- for at least 15 years after completion or discontinuation of the trial,

- or for at least two years after the granting of the last marketing authorization in the European Community (EC) and where there are no pending or contemplated marketing applications in the EC,

- or for at least two years after the formal discontinuation of clinical development of the investigational product.

Patient's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

13.0 REFERENCES

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Appendix I: ECOG Performance Status

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II: New York Heart Association Heart Failure Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

Appendix III: Further Guidance on the Definition of a Serious Adverse Event and Interpreting the Causality Question

Further Guidance on the Definition of a Serious Adverse Event

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g. hepatitis that resolved without hepatic failure).

Hospitalization

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g. bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Simply stopping the suspect investigational medicinal product (IMP) does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring i.v. hydrocortisone treatment,
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine,
- Intensive treatment in an emergency room or at home for allergic bronchospasm,
- Blood dyscrasias (e.g. neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization,
- Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the IMP.

1. Time Course. Exposure to suspect IMP. Has the patient actually received the suspect IMP? Did the AE occur in a reasonable temporal relationship to the administration of the suspect IMP?

2. Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect IMP (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
3. Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect IMP?
4. No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
5. Rechallenge experience. Did the AE reoccur if the suspect IMP was reintroduced after having been stopped? Rechallenge is not normally recommended or supported.
6. Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist. In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the IMP
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix IV: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Aprea Therapeutics AB's representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. Identification of potential hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in

combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. Follow-up

1.1. Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

1.2. Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6 of this Appendix)
- Notify the Theradex representative who will then inform Aprea Therapeutics AB

The Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Medical Monitor.
- Complete the relevant eCRF pages as information becomes available
- If at any time (in consultation with the Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. Review and Assessment of potential Hy's law cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Medical Monitor contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Medical

Monitor and Aprea Therapeutics AB will also be involved in this review together with other patient matter experts as appropriate.
According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the SAE reporting processes as defined in Section 7.3.4 of this protocol

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Theradex standard processes
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. Actions required when potential Hy's law criteria are met before and after starting study treatment

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.
At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

    - If there is no significant change no action is required

    - If there is a significant change notify the Theradex representative, , then follow the subsequent process described is Section 1.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Medical Monitor if there is any uncertainty.

7. Actions required for repeat episodes of potential hy's law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.
The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.
The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6 of this Appendix.

If No: follow the process described in Section 1.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 1.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Medical Monitor if there is any uncertainty.

8. References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix VI: GCIG CA-125 Response Definition

Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)

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Abstract: The Gynecological Cancer Intergroup (GCIG) has previously reached consensus regarding the criteria that should be used in clinical trial protocols to define progression-free survival after first-line therapy as well as the criteria to define response to treatment in recurrent disease using the serum marker CA 125 and has specified the situations where these criteria should be used. However, the publications did not include detailed definitions, nor were they written to accommodate the new version of Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.1) now available. Thus, we recommend that the definitions described later in detail are incorporated into clinical trial protocols to maintain consistency. The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated (Pujade-Lauraine, personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished. These definitions were developed from analyzing patients receiving cytotoxic chemotherapy and have not yet been validated in patients receiving molecular targeting agents.

Key Words: CA 125, Ovarian cancer, Response, Progression, RECIST, Clinical trials

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The Gynecological Cancer Intergroup has previously reached consensus regarding the criteria that should be used in clinical trial protocols to define progression-free survival after first-line therapy[1] as well as the criteria to define response to treatment in recurrent disease[2] using the serum marker CA 125, and have specified the situations where these criteria should be used (Table 1). However, the publications did not include detailed definitions nor were they written to accommodate the new version of Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.1) now

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TABLE 1. GCIG recommendations for CA 125 criteria for response and progression in various clinical situations

	Use Recommended by GCIG	Not Standard and Needs Further Validation	Not Recommended by GCIG
First-line trials	CA 125 progression		Ca 125 response
Maintenance or consolidation trials		CA 125 response and progression	
Relapse trials	CA 125 response and progression		

available.[3] Thus, we recommend that the definitions described later in detail below are incorporated into clinical trial protocols to maintain consistency. The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated (Pujade-Lauraine, personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished. These definitions were developed from analyzing patients receiving cytotoxic chemotherapy and have not yet been validated in patients receiving molecular targeting agents.

The GCIG recommends that for trials of relapsed ovarian cancer, the following definition for response according to CA 125 be used in addition to the updated RECIST 1.1[3] response criteria.

EVALUATION OF RESPONSE ACCORDING TO CA 125

Definition of Response

A CA 125 response is defined as at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA 125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA 125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA 125 response results from both treatment modalities. CA 125 cannot distinguish between the effects of the 2 treatments.

The date when the CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate response, an intent-to-treat analysis should be used that includes all patients with an initial CA 125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA 125 response and whose CA 125 level falls to within the reference range can be classified as CA 125 complete responders. In Tables 2 and 3 where CA 125 is stated as normalised or normal, means within the reference range. Patients who have a fall of CA 125 to within the reference range but whose initial CA 125 was less than twice the upper limit of the reference range have not had a CA 125 response and cannot therefore be classified as a CA 125 complete responder.

Evaluation of Response According to CA 125 in Patients Receiving First-Line Therapy

The CA 125 response definition was developed to evaluate response to chemotherapy in patients with recurrent ovarian cancer. If the patient has had combined modality therapy as part of their first-line therapy (eg, surgery and chemotherapy), CA125 response may be due to both or either treatments, and it should be clearly stated that CA125 cannot distinguish between the effects of the 2 treatments. It should be also be noted that for a patient to be classified as a complete responder according to RECIST, tumor marker levels such as CA 125 must be within the reference range.

Evaluation of Response According to CA 125 in Patients Receiving Maintenance or Consolidation Therapy

Patients whose CA 125 is greater than twice the upper limit of the reference range when they start maintenance or consolidation therapy can be evaluated using the GCIG CA 125 response definition. However, it should be noted that there are no data to validate the implications of achieving CA 125 response in this setting with respect to progression-free or overall survival. To prevent the prior therapy from interfering with the response assessment, we recommend that 2 pretreatment samples no more than 8 weeks apart are required if test treatment is given as part of maintenance or consolidation therapy. For the test treatment to be evaluable according to CA 125, there should be no more than a 10% fall in CA 125 between the 2 pretreatment samples. The sample closest in time to the test therapy should be considered the pretreatment sample.

TABLE 2. Evaluation of best overall response in patients *without* initial measurable disease and who are evaluable by CA 125

CA 125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized 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	

*Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
†Unequivocal progression in nontarget lesions may be accepted as disease progression.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Evaluation of Best Overall Response in Patients *Without* Initial Measurable Disease and Evaluable by CA 125

CA 125 may be used to evaluate response in patients without initial measurable disease either because no measurable disease is evident on radiological imaging or because appropriate imaging has not been performed as demonstrated in Table 2.

Evaluation of Best Overall Response in Patients *With* Initial Measurable Disease and Who are Also Evaluable by CA 125

A report that combines both CA 125 and RECIST 1.1 criteria is likely to include patients who are measurable by one or both of the criteria and who may have events at different time points. It should be determined according to Table 3. In patients who have measurable disease by both

TABLE 3. Best overall response in patients with measurable disease and who are also evaluable by CA 125

Target Lesion*	Nontarget†	New Lesion	CA 125	Overall Best Response	
CR	CR	No	Normal	CR	Best RECIST 1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days if response is primary end point
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 RECIST 1.1.
†Nontarget lesions include ascites and peritoneal thickening which are not measurable according to 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.
§The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.
NE, Not evaluated; NAE, not all evaluated.

TABLE 4. Example of reporting RECIST, CA-125, and combined response

	CA 125 Response			
RECIST	**Yes**	**No or PD**	**N/E**	**Total RECIST**
CR*	***4***	0	0	*4*
PR	***3***	*1*	*1*	*5*
SD	**3**	12	1	16
PD	0	8	2	10
NE	**3**	5	2	10
Total CA 125	**13**	26	6	Total entered = 45

In the above example, the RECIST 1.1 response rate is 9 (25.7%) of 35 RECIST 1.1 evaluable patients, the CA 125 response rate is 13 (33%) of 39 CA 125 evaluable patients, and the combined overall response rate (either RECIST or CA 125 response) is 15 (35%) of 43.

*RECIST 1.1 includes normalization of CA 125 to achieve CR (Table 3).

Bolded numbers, CA 125 responders; bolded and italicized numbers, both RECIST and CA 125 responders; italicized numbers, RECIST responders.

criteria, the date of response will be the date of the earlier of the 2 events if this approach to combined response reporting is to be used. In the combined assessment of CA 125 and RECIST 1.1 response, the following algorithm applies when determining the best overall response. If patients have progressive disease (PD) according to RECIST 1.1 within 28 days of CA 125 response, they are classified as having PD. If the PD according to RECIST 1.1 is longer than 28 days before or after the CA 125 response, they are classified as having partial response. Patients whose best response according to RECIST 1.1 is stable disease but who have a CA 125 response are classified as CA 125 responders.

REPORTING OF RESPONSE ACCORDING TO BOTH RECIST 1.1 AND CA 125 CRITERIA

Responses should be reported separately for both RECIST 1.1 and CA 125 response as shown in the hypothetical example in Table 4.

Definition of Progression on Therapy and Recurrence After Therapy According to CA 125

Progression (PD) is conventionally defined according to RECIST 1.1 but can also be based on serum CA 125 (defined below). However, in assigning the date of progression, PD by objective change in tumor size should always take precedence over CA 125 should it occur first. If measurable disease is reducing in size during treatment but the CA 125 results suggest progression (as defined below), the patient should continue to receive protocol treatment. If measurable disease is stable but CA 125 indicates confirmed progression over at

TABLE 5. Definition of progression after first-line therapy in ovarian cancer as proposed by the GCIG

GCIG Subcategorized Group	RECIST Measurable/Nonmeasurable Disease		CA 125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of diameters (RECIST 1.1 definition)	A N D	CA 125 ≥ 2 × ULRR documented on 2 occasions* Date of PD: first date of the CA 125 elevation to ≥ 2 × ULRR
	or		
	Any new lesions (measurable or nonmeasurable)	/	
	or		
	Unequivocal increase in nontarget disease		
	Date of PD: date of documentation of increase or new lesions		
B	As for A	O R	CA 125 ≥ 2 × nadir value on 2 occasions* Date of PD: first date of the CA 125 elevation to ≥ 2 × nadir value
C	As for A		As for A

GCIG groups A, B, and C defined above.

CA 125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days should not be taken into account.

*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.

least 4 weeks, some protocols may advise changing protocol treatment, unless there is the possibility that the therapy could be slowing the rate of rise of CA 125. If patients are having routine CA125 measurements as part of follow-up, the date of progression is likely to be several months earlier than symptoms or signs of progression develop.[6] Therefore, when categorizing patients according to time to progression, it is necessary to specify how the date of progression was defined (CA 125 alone, CA125 and symptoms, and RECIST). Protocols will need to specify that these data have to be collected.

EVALUATION OF PROGRESSION ACCORDING TO CA 125

Progression or recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125 according to the following criteria and Table 5:

A. Patients with elevated CA-125 pretreatment and normalization 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 *or*
B. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart *or*
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.

CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura (eg, paracentesis) during the previous 28 days.

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.

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Appendix VII: QOL Questionnaires

FACT-O (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-O (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-O (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
O1	I have swelling in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience any change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost any hair?	1	2	3	4
39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
40. Did food and drink taste different from usual?	1	2	3	4
41. Have you had tingling hands or feet?	1	2	3	4
42. Have you had numbness in your fingers or toes?	1	2	3	4
43. Have you felt weak in your arms or legs?	1	2	3	4
44. Did you have aches or pains in your muscles or joints?	1	2	3	4
45. Did you have problems with hearing?	1	2	3	4
46. Did you urinate frequently?	1	2	3	4
47. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48. Did you have hot flushes?	1	2	3	4
49. Did you have night sweats?	1	2	3	4

Please go on to next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
50. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51. Have you been dissatisfied with your body?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
55. To what extent were you interested in sex?	1	2	3	4
56. To what extent were you sexually active?	1	2	3	4

Answer the following two questions only if you were sexually active:

57. To what extent was sex enjoyable for you?	1	2	3	4
58. Did you have a dry vagina during sexual activity?	1	2	3	4