# 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

Published: 11-11-2015
Last updated: 19-04-2024

Primary Objective: * To make a preliminary assessment of the efficacy of a combined APR-246 and carboplatin/PLD chemotherapy regimen in patients with platinum sensitive recurrent HGSOC with mutated p53.Secondary Objective: * To assess the safety...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Reproductive neoplasms female malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47287

**Source**
ToetsingOnline

**Brief title**
PiSARRO

### Condition

- Reproductive neoplasms female malignant and unspecified
- Ovarian and fallopian tube disorders

**Synonym**
Patients with high grade serous ovarian cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Aprea Therapeutics AB
**Source(s) of monetary or material Support:** Industry - Aprea AB

## Intervention

**Keyword:** APR-246, Combination chemotherapy, High Grade Serous Ovarian cancer

## Outcome measures

### Primary outcome

Primary Endpoints

* Progression Free Survival (PFS), defined as the time from registration to the time of disease progression or relapse (according to RECIST 1.1 only) or death, or the date of last tumor assessment without any such event (censored observation).

### Secondary outcome

Secondary Endpoints

* PFS by assessment of CA 125 as a tumor marker.

* Overall Survival (OS), calculated as the time from registration to the date of death from any cause.

* Overall Response Rate (RR), calculated as the proportion of patients with a best overall response of confirmed Complete Response (CR) or Partial Response (PR).

* Safety profile (AEs, laboratory assessments and physical findings) of the combined APR-246 and carboplatin/PLD chemotherapy regimen or the carboplatin/PLD chemotherapy regimen alone.

* Evaluation of potential biomarkers.

* Biological activity in tumor and surrogate tissues.

# Study description

**Background summary**

High Grade Serous Ovarian Cancer (HGSOC) accounts for approximately 70% of malignant surface epithelial carcinoma in Europe and North America. Clinical data shows that p53 mutations are present in at least 96% of patients with HGSOC. Furthermore, p53 mutations have been shown to correlate significantly with resistance to chemotherapy, early relapse and shortened overall survival.

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 a improvement in PFS (11.3 months versus 9.4) with lower rates of severe and long-lasting side effects, and has been accepted as European standard of care for patients with platinum-sensitive ovarian cancer, including HGSOC.

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 p53 mutant ovarian cancer cell lines, resulting in resensitization of cancer cells to cisplatin.

**Study objective**

Primary Objective:
* To make a preliminary assessment of the efficacy of a combined APR-246 and carboplatin/PLD chemotherapy regimen in patients with platinum sensitive recurrent HGSOC with mutated p53.

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.

## Study design

This study is an open-label, multi-center Phase Ib/II proof-of-concept study with a dose confirmation component to assess whether patients with platinum sensitive recurrent p53 mutated 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.

All patients will have pre-screening IHC to determine p53 status and therefore eligibility. Archived sections from the original tumor sample will be reviewed by a gynecological pathologist to confirm the diagnosis of high grade serous ovarian cancer and positive nuclear IHC staining for p53. Patients without positive nuclear 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 Phase II will enroll 164 evaluable patients with p53 mutation. CT/MRI measurements using RECIST 1.1 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 should only be performed if clinical symptoms are suggestive of recurrence or there is CA 125 progression as defined by GCIG criteria (Rustin et al., 2011). Radiological tumor assessment should occur within 3 weeks of the date of suspected clinical or CA 125 progression. If there is CA 125 progression but no radiological documentation of disease progression then imaging should be repeated at least 3-monthly until protocol defined progression occurs. For patients with stable disease, follow-up will take place until disease progression or until death.
All scans should have the same modality (CT or MRI) but CT is preferred.

## Intervention

Intravenous infusion with APR-246 (dose tbc) on days 1-4 of each cycle. Maximum 6 cycles.
Intravenous infusion with Carboplatin (AUC 5) and Caelyx (30 mg/m2) on day 4 of each cycle. Maximum 6 cycles.

## Study burden and risks

In the completed Phase I clinical trial (APR-246-01) only a relatively few reported AEs (adverse events) were considered to be potentially related to treatment. From patients who received the 2-hour infusion of APR246 the most common related AEs related were fatigue, followed by dizziness, headache, and

confusion and other neurologic AEs such as muscle spasms and sensory disturbances. The treatment*related AEs typically occurred at the end of the infusion or shortly after the infusion and continued for hours or, in some cases, days. All AEs were reversible. No bone marrow toxicity was seen.

In a subsequent amendment to that study (Amendment 6), the duration of study drug administration was increased to be a 6-hour infusion to attempt to reduce and minimise the neurological AEs previously seen. Considering the patients* advanced disease, good tolerability was demonstrated. The number of reported AEs was limited and most events were considered as unlikely related to the APR-246 treatment. The AEs judged to have possible or probable relationship to the study treatment were single reports of dizziness, dyskinesia (Nervous system disorders), disorientation (Psychiatric disorders), fatigue (General disorders), electrocardiogram QT prolonged (Investigations) and osteonecrosis (Muscular and connective diseases).Two of these events, dyskinesia and electrocardiogram QT prolonged, reported by the same patient, were judged to be serious, related to the APR-246 treatment and not previously described or expected (i.e., SUSARs). Overall, APR-246 was well tolerated and with a safety profile very different from conventional chemotherapies.

A secondary centralized analysis of the ECGs collected from patients enrolled under Amendment 6 was done by a central laboratory. It concluded that there do not appear to be consistent, systematic, individual ECG changes after exposure to APR-246. Nonetheless, a small effect of APR-246 on the QTcF interval cannot be ruled out given the quality of the ECG database, and collection of digital ECG in triplicate format in a further trial is intended. A robust cardiac monitoring was therefore instigated in the Phase Ib part of the current, ongoing study in cycle 1. This included 12-lead ECG performed at baseline, Day 19 cycle 1 and before all other treatment cycles. The patients also have a 24 hour Holter ECG on Days 1 and 4 of APR-246 infusion for the first cycle. This data will is centrally analysed by Cardiabase and also reviewed by the Cohort Review Committee (CRC). This data has demonstrated that in Cohorts 1 and 2 there is no evidence of cardiac toxicity.

In line with the directive on risk mitigation (EMEA/CHMP/SWP/28367/07) the design of the trial takes into consideration possible unanticipated effects of APR-246 together with concomitant administration of carboplatin/PLD and, in the currently ongoing Phase Ib part of the study, a safety evaluation was performed by the treating investigator prior to each dosing within a cohort. The second and third cohorts were not initiated until all of the patients in the first cohort had been reviewed by the CRC.

The clinical data reviewed to date in the ongoing Phase Ib part of the study confirms that the nervous and the gastrointestinal systems are main potential target organs for toxicity. The treatment*related AEs typically occurred at the end of the infusion or shortly after the infusion and continued for hours or, in some cases, days. All AEs were reversible. The early evolving data from the

APR-407 study seems to suggest that APR-246 may potentiate the bone marrow suppression caused by chemotherapy. This finding is still under evaluation and will likely be clarified only in the randomised part of the study.

To date, the most frequently reported adverse events (regardless of severity) related to APR-246 study drug include fatigue, nausea, vomiting, dizziness, headache and taste changes. These events were also reported in the previous clinical trials as effects related to APR-246 monotherapy treatment. Haematological events (neutropenia, thrombocytopenia), and low grade CNS related effects (dizziness, vertigo, nausea, dysgeusia) have also been reported. No new safety concerns have emerged.

To date, patients have been enrolled in all three dose cohorts of the Phase Ib part of the study and the patients in the first cohort have completed therapy. In cohort 1, 2 patients were partially platinum sensitive and 1 sensitive. At least 5 patients have tolerated 6 cycles of treatment. One dose-limiting toxicity (DLT) of ruptured diverticulum has been reported (patient 004 in Cohort 2). This led to the expansion of this cohort to 6 patients.

Several patients in the current study have experienced neutropenia and thrombocytopenia, often requiring GCSF support in order to be able to continue with APR-246 and carboplatin/PLD treatment. Many patients experienced delays and/or dose reductions due to myelosuppression. No bone marrow toxicities were noted in the previous clinical studies with single agent APR 246. Myelosuppression is associated with carboplatin/PLD. It is too early to determine whether or not the severity of myelosuppression is increased with combination of APR-246 and carboplatin/PLD.

A single patient experienced a single episode of temporarily elevated hepatic enzymes; therefore, a safety update was distributed to all investigational sites. This was to advise caution when co-administrating APR-246 and full dose paracetamol (i.e. 4g/24hrs) based compounds, and that such compounds should be immediately terminated if any increase from baseline liver function tests were detected. The patient information sheets were also revised to include this theoretical risk.

The risks associated with drawing blood may include momentary discomfort and bruising. In rare cases, infection, excess bleeding, clotting or fainting may occur. The risks associated with biopsy may include numbness or tingling where the local anaesthesia is applied, temporary pressure and/or pain during the procedure, bleeding, bruising or soreness at the site after the sample is collected. Rarely, infection can develop. These effects, should they occur, will be managed per local hospital guidelines.

All patients will have their haematological, biochemical, vital signs and ECG parameters monitored. The eligibility criteria place more stringent than normal limitations on platelet count, white cell and especially lymphocyte count, AST

and ALT levels, bilirubin and albumin. Events considered possibly related to APR-246 will be evaluated and any appropriate changes to trial procedures or monitoring will be instituted.

The investigation of APR-246 in combination with carboplatin/PLD in this patient population is justified, based upon the clinical and nonclinical safety profile, the limitations of current treatments available to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation. Thus the benefit/risk assessment for this study supports the administration of APR-246 to patients with platinum sensitive, recurrent p53 mutated HGSOC to increase the efficacy of the platin based combination chemotherapy treatment.

Expected benefit:
The previous phase I study in patients demonstrated both the feasibility of administering potentially effective doses of APR-246 to humans and suggested APR-246 has a favourable safety profile compared with current cytotoxic therapies in practice. APR-246 exhibits linear pharmacokinetics up to the dosages administered. In patients, plasma concentrations consistently above those associated with effects in both ex vivo and in vivo pre-clinical models have been achieved. Thus, the feasibility of administering potentially effective doses of APR-246 in humans has been demonstrated.

Mutated p53 is a hallmark of HGSOC and correlates significantly with resistance to chemotherapy, early relapse and shortened overall survival. There is therefore a need for improved treatment of HGSOC since currently available therapies have little impact on survival. APR-246 may offer such an opportunity since p53 mutation is found in at least 90% of patients with late stage HGSOC (stage III * IV) at the time of diagnosis. APR-246 has been shown to induce apoptosis and cell death in cancer cells with mutant or otherwise non-functional p53 and has strong synergistic anticancer effects in combination with several conventional chemotherapeutic drugs including platinum-containing agents.

# Contacts

**Public**
Aprea Therapeutics AB

Karolinska Institutet Science Park, Nobels väg 3
Solna SE-171 65
SE
**Scientific**
Aprea Therapeutics AB

Karolinska Institutet Science Park, Nobels väg 3
Solna SE-171 65
SE

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## 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) * 1.5 x109/L,
* Platelets * 100 x109/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:
o Oral
o Intravaginal
o Transdermal ;* Progestogen-only hormonal contraception associated with inhibition of ovulation:
o Oral
o Injectable
o 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/m2 or epirubicin >720 mg/m2.
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 (< 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.
15. Use of concomitant treatment with QT/QTc prolonging drugs.

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 06-09-2016 |
| Enrollment: | 29 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | APR-246 |
| Generic name: | 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo[2,2,2]octan-3-one |
| Product type: | Medicine |
| Brand name: | Caelyx |
| Generic name: | Doxorubicin |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Carboplatin |
| Generic name: | Carboplatin |
| Registration: | Yes - NL intended use |

# Ethics review

| | |
|---|---|
| Approved WMO Date: | 11-11-2015 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 06-04-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 01-06-2016 |

| | |
|---|---|
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 27-07-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 03-08-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 28-12-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 05-01-2017 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 25-09-2017 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 15-12-2017 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 20-07-2018 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

| | |
|---|---|
| Approved WMO Date: | 30-08-2018 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 12-09-2018 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2013-001472-38-NL |
| ClinicalTrials.gov | NCT02098343 |
| CCMO | NL53070.068.15 |