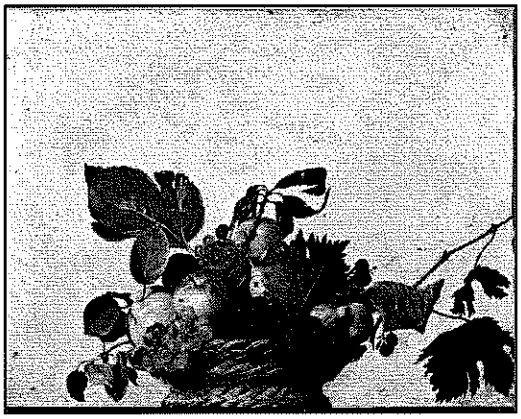
CLINICAL STUDY PROTOCOL

The BAROCCO study (Best Approach in Resistant-Ovarian-Cancer with-Cediranib-Olaparib): an Italian multicenter randomized phase II study of weekly paclitaxel vs. Cediranib-Olaparib with continuous schedule vs. Cediranib-Olaparib with intermittent schedule in patients with platinum resistant high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.



Basket of fruit - Michelangelo Merisi da Caravaggio 1599, Ambrosian Library, Milan –

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SUPPORTED BY	AstraZeneca
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INVESTIGATOR AGREEMENT

This study is a Phase II, open label, multicentre study assessing the efficacy and safety of Olaparib and Cediranib combination in the treatment of platinum resistant ovarian cancer comparing continuous versus intermittent schedule.

Sponsor and author approval:

This clinical study protocol has been reviewed and approved by a Sponsor Representative and the Principal Investigator.

Roldano Fossati (Sponsor Representative) _____ 11-10-2016

Signature Date

Nicoletta Colombo (Principal Investigator) _____ 11.10.2016

Signature Date

Investigator signature:

I have read the contents of this protocol and I agree to abide by all provisions set for therein.

I agree to personally conduct or supervise this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki and with the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable local regulatory requirements.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. I agree to make available to sponsor personnel, their representatives and relevant regulatory authorities, my subject's study records in order to verify the data that I have entered into the case report forms.

_____ _____ _____

Print name Signature Date

PROTOCOL SYNOPSIS

Title	**The BAROCCO study (Best Approach in Recurrent-Ovarian-Cancer-with Cediranib-Olaparib):** an Italian multicenter randomized phase II study of weekly paclitaxel vs. Cediranib-Olaparib with continuous schedule vs. Cediranib-Olaparib with intermittent schedule in patients with platinum resistant high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.
Sponsor	Mario Negri Gynecologic Oncology Group (MaNGO) IRCCS - Istituto di Ricerche Farmacologiche Mario Negri Via La Masa, 19 20156 Milano (Italy)
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Clinical Phase	II
Background and Rational	About one-fourth of ovarian cancer first relapses are platinum resistant (patients whose disease relapses within 6 months after platinum based chemotherapy) or refractory. Combination-non-platinum based chemotherapy failed to show any clinical benefit in comparison to single agent chemotherapy with weekly paclitaxel being currently considered one of the best therapeutic option in platinum and bevacizumab resistant patients. In platinum resistant but bevacizumab naïve patients, AURELIA trial showed a statistically significant increase in PFS (but not in OS) when bevacizumab was combined with non-platinum single agent chemotherapy Cediranib (an oral VEGFR TK inhibitor) and Olaparib (an oral PARP inhibitor) have singly showed clear activity in ovarian cancer throughout several clinical settings. Cediranib showed to be effective for the treatment of platinum-sensitive recurrent OC with PFS and OS benefits. Olaparib was demonstrated to be effective for both BRCA1-2 mutated and wild-type tumors. Thus, Cediranib and Olaparib combination is theoretically attractive. A recently published phase II trial in women with platinum sensitive disease showed promising results (Liu J et al.). In particular and unexpectedly, patients without or with unknown BRCA mutations experienced a greater benefit from Cediranib plus Olaparib compared with Olaparib. A smaller trend

	towards increased PFS was observed in patients with BRCA1-2 mutations Moreover, in xenograft models the inhibition of VEGFR-3 may represent a therapeutic means to down-regulate BRCA expression in BRCA wild type tumors, thus making them mimic BRCA deficient tumors. These data suggest a possible synergistic effect of Cediranib and Olaparib for restoring PARP inhibitor activity in BRCA wild-type tumors. To our knowledge, there are no data about the efficacy of this combination therapy in platinum resistant/refractory disease. Thus, the purpose of this study is to test the combination of Olaparib/Cediranib in platinum resistant/refractory disease, comparing this regimen with traditional chemotherapy. The control group will be treated by weekly paclitaxel. The safety and efficacy of Olaparib has been demonstrated in the clinical programs using predominantly the capsule formulation (400 mg [8 capsules] twice daily as monotherapy). However, an improved tablet formulation has been developed. Thus, since the dosage of 300 mg twice daily in tablet formulation was characterized by similar efficacy and tolerability compared to 400 mg twice daily in capsule formulation, the dosage of Olaparib chosen for the study is 600 mg tablet (300 mg twice daily). Regarding Cediranib, the dosage chosen in this study is 20 mg, usually suggested when the drug is combined with other agents (from ICON 6 study that tested Cediranib as concurrent and manteinance therapy). As reported in the same study by Liu J et al., the most frequent grade III or higher AEs in the Cediranib/Olaparib combination arm compared to control regimen consisted not only in hypertension but in diarrhea and fatigue also, suggesting an amplificatory effect caused by Cediranib. Thus, the identification of a less toxic and equally effective schedule of administration of this combined regimen represents an important issue. In the attempt to reduce the combination toxicity and considering that

	an intermittent schedule has been successfully applied to other TKI, in particular sunitinib, we decided to test a 5-day out of 7 schedule. We expect that such schedule could prevent prolonged drug interruptions due to severe toxicity of the continuous schedule thus allowing a better dose intensity and optimal drug activity. Moreover, as the median half-life of Cediranib is quite long, but the cytokine release induced by VEGFR-1, VEGFR-2, VEGFR-3 is short-lasting, a 5-day out of 7 schedule may allow a better therapeutic index. Thus, due to these considerations, this study proposes to test the efficacy of the combination both with continuous and intermittent schedule.
Study objectives *Efficacy* - *Primary*	The study primary objective is to compare the efficacy of Olaparib and Cediranib vs. weekly paclitaxel in terms of progression free survival (PFS) in platinum refractory or resistant recurrent ovarian cancer. PFS is defined as the time from randomization to the date of first progression or death for any cause, whichever comes first. Progression will be established as the objective radiological disease progression according to RECIST 1.1 or to clinical assessment.
- *Secondary*	Secondary objectives are : - Objective Response Rate (ORR), defined as the percentage of patients with an objective response as determined by RECIST 1.1 - PFS2 defined as time from randomization to second disease progression according to RECIST 1.1 or to clinical assessment, or death by any cause. - Overall Survival (OS), defined for each patient as the time from randomization to the date of death for any cause. - Quality of Life evaluated by the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire.
Safety	

- *Primary* - *Secondary* *Compliance*	The primary objective for safety is to compare the safety of Olaparib and Cediranib as intermittent vs. continuous regimen in terms of number of evacuations per day. Secondary objectives are : Maximum toxicity grade experienced by each patient, for each toxicity, according to NCI-CTCAE v. 4.0; patients experiencing grade 3-4 toxicities for each toxicity; type, frequency and nature of SAEs; patients with at least a SAE; patients with at least a SADR; patients with at least a SUSAR. Compliance will be evaluated in terms of: number of administered cycles; reasons for discontinuation and treatment modification; dose intensity.
Study design	This is a Phase II, randomized, multi-centre study with two experimental arms, Cediranib-Olaparib with continuous schedule and Cediranib-Olaparib with intermittent schedule. Weekly paclitaxel is the comparator arm, due to its known efficacy in platinum resistant/refractory disease. All patients not previously tested for the presence of BRCA1-2 germline mutations will undergo BRCAtest. However, both mutated and not mutated women will be included in the study protocol. Randomization will use a biased-coin minimization procedure having as stratification factors BRCA1-2 genes status (mutated vs. wilde-type vs. still unknown), prior chemotherapy (1-2 vs. $\geq$ 3 lines) and previous treatment with antiangiogenic drugs (yes vs. no). Cross-over of the patients assigned to the control arm to the experimental arms, at disease progression, is not allowed.
Patient number	90 patients evaluable for the primary analysis.
Target population *Inclusion criteria*	For inclusion in the study patients should fulfill the following criteria: **1.** Patients affected by pathologically confirmed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. **2.** Relapsed/progressive disease within 6 months from last

platinum-based chemotherapy (platinum resistant/refractory disease).

3. Any line of treatment (after the first).
4. Any "last" chemotherapy line, including Paclitaxel, that should have been administered at least 6 months before the study beginning.
5. Patients must be women ≥ 18 years of age.
6. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
   - Haemoglobin ≥ 10.0 g/dL and no blood transfusions in the 28 days prior to entry/randomization - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - White blood cells (WBC) > 3x10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional Upper Limit of Normal (ULN)
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional Upper Limit of Normal, unless liver metastases are present in which case it must be ≤ 5x ULN
   - Creatinine clearance estimated using the Cockcroft-Gault equation ≥51 mL/min,.
7. ECOG performance status 0-1.
8. Patients must have a life expectancy ≥ 16 weeks.
9. Evidence of non-childbearing status for women of childbearing potential (negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1 or postmenopausal women. Postmenopausal status is defined as:
   -Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
   -LH and FSH levels in the post-menopausal range for women under 50
   -Radiation-induced oophorectomy with last menses >1 year ago,
   -Chemotherapy-induced menopause with >1 year interval since last menses
   -Surgical sterilization (bilateral oophorectomy or hysterectomy).
10. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment, scheduled

	visits and examinations including follow up. **11.** At least one lesion (measurable as defined by RECIST 1.1) that can be accurately assessed by CT scan or MRI with Chest X-ray at baseline and follow up visits. 12. BRCA1-2 mutation status known. In case of BRCA status unknown, the BRCA test must be performed before the randomization or, if not feasible, within the end-of the study treatment. **13.** Provision of informed consent prior to any study specific procedures. In case of patients unable to give written informed consent, is necessary to have the subject or legal representative sign, but in any case a witness must be present and sign and date with the person providing informed consent.
Exclusion criteria	Patients should not enter the study if any of the following exclusion criteria are fulfilled: **1.** Any previous treatment with a PARP inhibitor, including Olaparib. **2.** Prior treatment with Cediranib (previous bevacizumab or other antiangiogenic drugs are allowed) **3.** Previous progression to weekly Paclitaxel **4.** Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for $\geq$ 5 years **5.** Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment with study drug. **6.** Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir,

	saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting Olaparib is 2 weeks. **7.** Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting Olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. **8.** Persistent toxicities (>=CTCAE grade 2) with the exception of alopecia, caused by previous cancer therapy. **9.** Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome. **10.** Greater than +1 proteinuria on two consecutive dipsticks taken no less than 1 week apart unless urinary protein < 1.5g in a 24 hr period or urine protein/creatinine ratio < 1.5. **11.** A history of poorly controlled hypertension or resting blood pressure >150/100 mmHg in the presence or absence of a stable regimen of anti-hypertensive therapy (measurements will be made after the patient has been resting supine for a minimum of 5 minutes. Two or more readings should be taken at 2-minute intervals and averaged. If the first two diastolic readings differ by more than 5 mmHg, then an additional reading should be obtained and averaged). **12.** Blood transfusions within 28 days prior to study start. **13.** Features suggestive of Myelodysplastic syndrome or Acute myeloid leukemia (MDS/AML) on peripheral blood smear. **14.** Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 28 days prior to treatment. **15.** Major surgery within 4 weeks of starting study treatment and patients must have recovered from any effects of any major surgery. **16.** Patients considered at poor medical risk due to a serious,

	uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression (untreated and unstable for at least 28 days prior to study entry), superior vena cava syndrome, extensive bilateral lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent. **17.** Patients unable to swallow medications and patients with gastrointestinal disorders likely to interfere with absorption of the study medication. **18.** Breast feeding women. **19.** Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy. **20.** Patients with known active hepatic disease (i.e., Hepatitis B or C). **21.** Patients with a known hypersensitivity to Olaparib, Cediranib or any of the excipients of the products. **22.** Patients with a known hypersensitivity to Paclitaxel. **23.** Patients with uncontrolled seizures. **24.** History of abdominal fistula or gastrointestinal perforation. **25.** Prior gastrectomy.
Length of study	The study length should be 30 months: 18 months of accrual and 12 of follow-up.
Treatment regimens	Patients will be randomized in a 1:1:1 ratio to the treatments as specified below: • Paclitaxel 80 mg/mq every week. • Cediranib 20 mg/day + Olaparib 600 mg/day (300 mg twice daily) given every day. • Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg/day (300 mg twice daily) given 7 days per weeks. Treatment will be continued until progression, unacceptable toxicity, patient or physician decision to discontinue or death with maximum 24 weeks (6 cycles) in the Paclitaxel arm.
Statistical Methods	Assuming a median PFS in the control arm of 3.4 months (AURELIA trial control group), this study is designed to detect a HR of 0.51 that

	corresponds to an advantage in PFS median of 3.3 months. With one-sided 5% significance level and with at least 80% power, approximately 60 patients (55 events) for each comparison are estimated to be enrolled. Considering the two pre-planned comparisons (intermittent schedule vs Paclitaxel and continuous schedule vs Paclitaxel) a total of 90 eligible patients are needed. Taking into account a 10% of patients not evaluable for the primary endpoint, it will be necessary to enroll approximately 100 patients. A better toxicity profile (especially intestinal tolerability) for the intermittent schedule than the continuous schedule is plausible but lacks empirical evidence. A mean reduction of two evacuations a day over the first four weeks of treatment can be considered as clinically relevant. Considering the number of patients required for the PFS comparison, an effect size equal to 1 (assuming a standard deviation equal to 2) could be detected with a power greater than 90% and a one sided first-type error (alpha) equal to 5%. Since the comparison in safety will be performed only if both experimental arms demonstrate the superiority in terms of PFS over the control arm, an alpha adjustment is not required. Summarizing, when the target number of events for PFS will be reached, the following conclusions will be possibly drawn: - if both armsdemonstrate the superiority over control arm in terms of PFS, the best schedule will be selected based on safety profile considering in particular the mean number of evacuations per day - if only one experimental armdemonstrate the superiority over control arm in terms of PFS, there will be the positive effect only for that treatment schedule - if both armsdo not demonstrate the superiority over control arm in terms of PFS, there will be less than desired effect for both experimental arms and the combination of Cediranib and Olaparib will not be considered for further studies in this set of patients

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

ADR: Adverse Drug Reaction

AE: Adverse event

AESI: Adverse events of special interest

AIFA: Agenzia Italiana del Farmaco

ALP or AP: Alkaline phosphatase

ALT: Alanine Aminotransferase

AML: Acute Myeloid Leukaemia

ANC: Absolute neutrophil count

APTT: Activated Partial Thromboblastin Time

AR: Adverse Reaction

AST: Aspartate Transaminase

BD: Twice daily

BP: Blood Pressure

BRCA mutation or BRCAm: Breast Cancer susceptibility gene mutation (see gBRCA mutation or gBRCAm)

BRCA: Breast Cancer susceptibility gene

BSA: Body Surface Area

BUN: Blood Urea Nitrogen

CA-125: Cancer Antigen – 125

CCB: Calcium Channel Blocker

CDMA: Clinical Data Management Application

CHF: Congestive Heart Failure

CI: Confidence Interval

CNS: Central Nervous System

CR: Complete Response

CrCl: Calculated Creatinine Clearance by Cockcroft-Gault

CT: Computed Tomography

CTC: Common Toxicity Criteria

CTCAE: Common Terminology Criteria for Adverse Events

CT-3: good clinical practice in the conduct of clinical trials on medicinal products for human use.

CYP, CYP450: Cytochrome P450 (1A2, 3A4, 3A5, 2B6, 2C9, 2C19 and 2D6 refer to isoforms)

DCF: Data Clarification Forms

DHP: Dihydropyridine Calcium Channel Blocker

DLT: Dose-Limiting Toxicity

DSBs : DNA Double Strand Breaks

EC: Etichs Committee(s)

ECG: Electrocardiogram

eCRF: Electronic Case Report Form

ECOG: Eastern Cooperative Oncology Group

EE: Norelgestromin/ethinyl estradiol

EMA: European Medicines Agency

FACT-O: Functional Assessment of Cancer Therapy-Ovarian

FHS: Follicle-Stimulating Hormone

gBRCA: Germline BRCA

gBRCA mutation or gBRCAm: The term "gBRCA mutation" is used to refer to a germline BRCA1 or BRCA2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants.

gBRCA wt: gBRCA wild type

GCP: Good Clinical Practice

GCIC: Gynecological Cancer Intergroup

G-CSF: Granulocyte Colony-Stimulating Factor

GI: GastroIntesinal

GMP: Good Manufacturing Practice

Hb: Haemoglobin

Hct: haematocrit

HIV: human immunodeficiency virus

HGSOC: High Grade Serous Ovarian Cancer

HR: Hazard Ratio

HRT: Hormone Replacement Therapy

HRCT: High Resolution Computed Temography

HRD: Homologous Recombination Deficiency

HRR: Homologous Recombination Repair

H1 and H2 receptor antagonists: H_1 antagonists, also called H_1 blockers, are a class of medications that block the action of histamine at the H_1 receptor, helping relieve allergic reactions – H2 antagonists, also called H2 blockers, are a class of medications that block the action of histamine at the histamine H2 receptors of the parietal cells in the stomach. Both are a type of antihistamine.

IB: Investigators Brochure

IDMC: Independent Data Monitoring Committee

ICF: Informed Consent Form(s)

ICH: International Conference of Harmonisation

ICH E2A: Clinical Safety Data Management: definitions and Standards for Expedited Reporting"

IEC: Independent Ethics Committee

IEO: Istituto Europeo di Oncologia (di Milano)

IP: Internet Protocol

IRB: Institutional Review Board(s)

ISF: Investigator Site File(s)

ITT: Intent to Treat

IUD: Intrauterine Device

INR: International Normalised Ratio

KM: Kaplan-Meier method

LDH: Lactate Dehydrogenase

LH: Luteinizing Hormone

MAH: Marketing Authorization Holder

MATE1, MATE2K: Multidrug and Toxin Extrusion, 1, 2k

MCV: Mean Cell Volume

MDS: Myelodysplastic syndrome

MRI: Magnetic Resonance Imaging

NCI: National Cancer Institute

NTL: Non-Target Lesions

OATP, OATP1B1, OAT3: Organic Anion-Transporting Polypeptide, 1B1, 3

OC: Ovarian Cancer

OCT, OCT1, OCT2,: Organic Cation Transport 1-2

ORR: Overall Response Rate

OS: Overall Survival

PARP: Poly-ADP Ribose-Polymerisation

PARPi: PARP inibitor

PD: Progression of Disease

PFS: Progression Free Survival

PFS2: Progression Free Survival 2

P-gp: permeability glycoprotein

PI: Principal Investigator(s)

PK: Pharmacokinetic

PLD: Pegylated Liposomal Doxorubicin

PP: Per-Protocol

PR: Partial Response

PRES: Posterior Reversible Encephalopathy Syndrome

PRO: Patient-reported outcome

QOL: Quality of life

QT: A measurement of the time between the start of the Q wave and the end of the T wave in an ECG

QTc: QT interval corrected

QTcF: QT interval corrected for heart rate using Fridericia's formula

RECIST: Response Evaluation Criteria in Solid Tumors

RI: Reticulocyte Index

RPLS: Reversible Posterior Leukoencephalopathy Syndrome

R&D: Research & Development

SADR: Safety Adverse Drug Reaction

SAE: Serious adverse event

SAR: Serious Adverse Reaction

SC: Study Coordinator

SD: Stable Disease

SGOT: Serum Glutamic-Oxaloacetic Transaminase

SGPT: Serum Glutamic Pyruvic Transaminase

SIV: Site Initiation Visit

SmPC: summary of product characteristics

SOP: Standard Operating Procedure(s)

SSBs: Single Strand Breaks

SUSAR: Suspected Unexpected Serious Adverse Reaction

t-AML: therapy-related acute myeloid leukemia

tBRCAm: somatic BRCA mutations

TKI: Tyrosine Kinase Inhibitor

TOI: Trial Outcome Index

TSH: Thyroid stimulating hormone

TTP: Time To Progression

T3: Triiodothyronine

T4: Thyroxine

ULN: Upper Limit of Normal

US SEER:Untited States Surveillance, Epidemiology, and End Results

VEGF: Vascular endothelial growth factor

VEGFR: Vascular endothelial growth factor receptor

WBC: White blood cell(s)

WMA General Assembly: World Medical Association General Assembly

WNL: Within Normal Limits–see

1. INTRODUCTION

1.1 Background

Ovarian cancer (OC) represents the most lethal tumor among gynecologic malignancies. It accounts for about 239.000 new cases and 152.000 deaths worldwide [1]. Optimal surgery is the most important prognostic factor. However, even if first line chemotherapy with tri-weekly paclitaxel/carboplatin is highly active, with an overall response rate (ORR) >75%, most of the patients recurs and only 10-30% of them experience long term survival [2]. Approximately 90% of ovarian tumors are epithelial, with papillary serous histology accounting for 75% of all cases. Of these, 70% are high grade (type II) and share the same origin and clinical course with fallopian tube or primary peritoneal cancer [3]. Patients who do not respond to platinum chemotherapy (platinum refractory) and those presenting relapse within 6 months after the end of the last platinum treatment (platinum resistant) need further chemotherapy with non-cross resistant drugs. Among drugs available for resistant and refractory ovarian cancer, four agents are most commonly used, usually given as single agents, since the superiority of any combination chemotherapy has not been proven. These are pegylated liposomal doxorubicin, paclitaxel, topotecan and gemcitabine. Randomized phase III trials have reported similar rates of tumor response (range 10–15), progression free survival (PFS) of 3–4 months and OS of about 12 months [4-11]. Thus, new strategies are needed. In particular, scientific evidences showed that Paclitaxel seemed to be more effective when given weekly and that part of this additional benefit may be due to an antiangiogenic effect [12-19].

Angiogenesis, the process of new blood vessel formation, plays an important role in the development of malignancy as well as the growth and progression of metastatic lesions. Numerous growth factors and cytokines are involved in the angiogenic process that accompanies carcinogenesis. Among these factors, the Vascular Endothelial Growth Factor (VEGF) has a predominant role acting as an endothelial cell-specific mitogen. In addition to being a mitogenic and survival factor for endothelial cells, it is also a potent inducer of endothelial cell migration, invasion, vascular permeability, and vessel formation. Elevated VEGF expression at advanced stages of disease has been reported in various cancer types including breast, endometrial, ovarian, bladder, and lung cancers. Anti-angiogenic therapies showed to be active in OC with limited toxicities. Single agent bevacizumab has a response rate of 18% in recurrent OC. Recently, the results of a phase III trial with Bevacizumab were published (AURELIA) showing a PFS increase from 3.4 months with chemotherapy alone to 6.7 months with bevacizumab-containing therapy. ORR was 11.8% versus 27.3%, respectively. Although the combination arm with bevacizumab in AURELIA trial showed clear superiority in terms of PFS over the chemotherapy only arm, overall survival did not

differ [20]. Therefore chemotherapy alone can still be considered the standard of care in platinum resistant patients. Cediranib (AZD2171) is an oral, potent small-molecule inhibitor of several tyrosine kinases (TKI) including VEFGR-1, VEGFR-2, VEGFR-3 and c-kit. A phase I study of Cediranib showed a maximum tolerated dose of 45 mg and anticancer activity. A phase II trial showed that Cediranib as monotherapy has activity in recurrent epithelial OC, fallopian tube or peritoneal cancer obtaining a 19% response rate; due to the toxicities the dose was lowered to 30 mg daily. At the European Cancer Conference in 2013, Ledermann *et al.* presented a phase III trial designed to evaluate the safety and efficacy of platinum-based chemotherapy in combination with Cediranib, 20 mg daily, that then was continued as maintenance therapy in women with platinum-sensitive relapsed OC. The results showed a median PFS of 9.4 months in the chemotherapy arm and 11.4 months in the Cediranib maintenance arm (HR, 0.68; p = .002) and the median OS reached 17.6 months in the chemotherapy arm and 20.3 months in the Cediranib maintenance arm (HR, 0.70; p = .042). The conclusions were that Cediranib given concurrently with platinum-based chemotherapy improves PFS and, when continued as maintenance therapy, significantly improves both PFS and OS in women with recurrent OC [21].

Another important risk factor for OC is genetic predisposition derived from Breast Cancer Susceptibility Gene Mutation (BRCA1-2: gBRCAm) which accounts for the majority of hereditary OC. If a lifetime risk for OC among women in the general population is estimated to be 1.4%(14 out of 1,000), a woman with BRCA1 or BRCA2 deleterious mutation has a lifetime risk of 15 to 40% (150–400 out of 1,000); moreover BRCA mutated OC patients can also develop OC earlier in their life than those without the mutation [22]. Deficiency in BRCA ultimately leads to the accumulation of genetic alterations as a result of the failure of cells to arrest and repair DNA damage or to undergo apoptosis, resulting in tumorigenesis. If all OC patients underwent germinal BRCA testing (gBRCA), current estimates indicate that 13% to 14% of the overall OC population would have gBRCA1/2 mutations and the proportion of patients with gBRCA mutations may be as high as 22% in patients with high-grade serous OC (HGSOC). In addition, a population of OC patients whose tumors harbor BRCA1 and BRCA2 mutations that are not detected in the germline (~7%) also exist and are defined as somatic BRCA mutations (tBRCAm).

Patients with BRCA-mutated OC currently have identical treatment options as sporadic OC patients. They seem to have a better prognosis compared with the overall relapsed OC patient population but the pattern of disease is similar, with patients eventually dying from their disease. OC patients with BRCA mutation represent a small, well-defined and medically recognized subpopulation for whom, despite the potential for personalized healthcare, no targeted treatment currently exists.

Olaparib (AZD2281, KU-0059436) is a poly-ADP ribose-polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy

(including maintenance) and for combination with chemotherapy and other anti-cancer agents. PARP inhibition is a novel approach to target tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HRR). Tumors with homologous recombination deficiencies (HRD), such as serous OC and breast cancers cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, Olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens. Olaparib has been shown to inhibit selected tumor cell lines *in vitro* and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to Olaparib treatment. PARP inhibitors such as Olaparib may also enhance the DNA damaging effects of chemotherapy [23-25]. BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models *in vivo* [26] and in the clinic [27]. The mechanism of action for Olaparib results from the trapping of inactive PARP onto the single-strand breaks, thus preventing their repair [28,29]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous recombination repair.

Thus, PARP-inhibitors have been studied most extensively in HGSOC, with efficacy noted especially in platinum-sensitive high-grade serous OC. In particular, remarkable benefit was demonstrated in a randomized Phase 2 study of Olaparib versus placebo administered as maintenance after completion of platinum-based chemotherapy to women with platinum-sensitive HGSOC. The median progression-free survival (PFS) increased from 4.8 months to 8.4 months in the cohort as a whole (HR 0.35, $p = 0.001$). This difference was more striking in a group including g*BRCA*m patients and those with somatic *BRCA1/2* mutations, in which median PFS was increased from 4.3 months to 11.2 months (HR 0.18, $p < 0.00001$) [30]. However, results from this trial, as confirmed by other scientific evidences, demonstrated that this agent is potentially active in BRCA wild type tumors (gBRCA wt) also [30,31]. After the publication of these data, Olaparib was approved by the European Medicines Agency (EMA) as maintenance therapy in patients with BRCA mutation and platinum-sensitive relapsing OC in response to platinum based chemotherapy.

Two other important studies evaluating Olaparib as single agent should be mentioned. Kaye et al study randomized 97 patients (with confirmed germline BRCA1/2 mutation, OC that recurred or progressed within 12 months of the most recent platinum-based chemotherapy regimen) in an open-label phase II dose-finding study of Olaparib monotherapy (200 mg twice

daily [bd] and 400 mg bd capsule) vs. pegylated liposomal doxorubicin (PLD) [32]. The primary analysis of PFS (Investigator assessment) comparing both doses of Olaparib to PLD did not demonstrate a statistically significant difference (n=81, HR=0.88 95% CI (0.51, 1.56), median PFS 6.5 months, 8.8 months and 7.1 months for the Olaparib 200 mg, Olaparib 400 mg and PLD groups. Objective response rates were 25%, 31% and 18% for the Olaparib 200 mg, 400 mg and PLD groups respectively but these data are not reported by prior platinum status (even of the 50% of included patients had platinum resistant disease).

Kaufman et al study [33] enrolled 193 patients with platinum-resistant relapsed OC (including fallopian tube and primary peritoneal) and showed that Olaparib is active as monotherapy in patients with platinum-resistant disease with an overall response rate of 31%.

Preclinical and clinical data are now supporting the combination of Cediranib and Olaparib as potentially synergistic in the treatment of OC. In xenograft models the inhibition of VEGFR-3 may represent a therapeutic means to downregulate BRCA expression in gBRCA wt tumors, thus making them mimic BRCA deficient tumors. The use of VEGFR-3 inhibitors (such as Cediranib) in combination with PARP inhibitors (such as Olaparib) may restore PARPi activity in gBRCA wt tumors [34].
Clinical data are now supporting this hypothesis. Recently, Liu J et al published the results of a randomized phase II study in platinum sensitive OC patients, comparing Cediranib 30 mg daily in combination with Olaparib 200 mg bd vs Olaparib 400 mg bd. The combination of Olaparib and Cediranib was found significantly more active than Olaparib alone. Median PFS was 17.7 months with the combination treatment vs. 9 months with Olaparib alone. The superiority of the combined regimen was particular evident in patients with gBRCA wt tumors: median PFS was 16.5 months for the combination and 5.7 months for Olaparib alone [35]. This observation seems to confirm the synergistic effect of Cediranib and Olaparib previously described in xenograft models and support the rational for the use of this combination even in patients without BRCA mutation.
Regarding the safety, in general, the tolerability profile of Olaparib is well characterized and suitable for long-term dosing until disease progression in patients with relapsed platinum sensitive OC who carry gBRCAm. The common AEs of Olaparib include nausea, vomiting, fatigue and anemia. The low grade and intermittent nature of these events means that nausea and vomiting can be treated empirically and anti-emetic prophylaxis is not required. Hematological changes including anemia should be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients receiving anti cancer therapies. Where necessary, AEs can be managed by interrupting or reducing the Olaparib dose, treating symptomatically with standard procedures (eg, antiemetics for nausea and vomiting, occasional blood transfusions for anemia) or in rare cases by permanently discontinuing Olaparib treatment. Long-term tolerability to Olaparib maintenance therapy has

been demonstrated, with 45%, 25% and 17% of the patients in the gBRCA subgroup in study 19 in the Olaparib arm remaining on treatment at 1 year, 2 years and 3 years, respectively [30]. Most patients remained on treatment until disease progression, with only a small number of patients permanently discontinuing study treatment due to AEs (9.4% with Olaparib vs. 0% with placebo in the gBRCA subgroup).

Myelodysplastic syndrome and the development of acute myeloid leukemia (MDS/AML) are considered AEs of special interest as they may be related to agents that affect DNA repair, including chemotherapy. These events have been seen in less than 1% of patients who received Olaparib. These events will be actively monitored in the ongoing phase III studies, including prompted follow-up. Development of secondary myelodysplastic syndrome (MDS)/therapy-related acute myeloid leukemia (t-AML) is an AE of interest associated to Olaparib, as it may be related to products that affect DNA repair mechanisms. As of 20 August 2014, 21 reports of MDS/AML have been received out of 2,866 Olaparib treated patients, giving a cumulative reporting rate of 0.7%. Across the clinical study program, MDS has also been reported for 2 patients who did not receive Olaparib: one patient that received placebo in the study of Ledermann [30] (0.8% [1/128]) and one patient treated with pegylated liposomal doxorubicin as the comparator in the study of Kaye (3.1% [1/32]), giving a similar reporting rate [32]. Of the 21 cases reported across the development program, 14 have been reported in monotherapy studies and 7 in combination studies. Sixteen of the patients had a gBRCA mutation. In 13 cases, the diagnosis was MDS without a report of AML. There were 8 cases of AML. The median age of onset was 63 years and all but 3 patients had OC. Eight patients had a history of previous cancer. The mean time from diagnosis of current cancer to onset of MDS or AML was 62 months. All patients had associated history features that may have contributed to the development of MDS/AML. All had received chemotherapy with DNA damaging agents, including platinum, taxanes and anthracyclines. Many patients received multiple treatment regimens over multiple years and 7 patients had also received radiotherapy. Four patients were treated with Olaparib for less than 6 months, 5 patients were treated for between 6 months and 1 year, 4 patients were treated for between 1 and 2 years, and 8 patients were treated for more than 2 years. In the majority of cases, MDS occurred while on treatment with Olaparib but in 4 cases the onset of MDS was more than 5 months after Olaparib was discontinued. Epidemiological studies from the literature have indicated a higher risk of therapy related AML in OC populations, particularly those receiving alkylating agents and pelvic irradiation with a wide range of incidence rates. In two recent studies using the US SEER database, Vay et al. identified 98 cases of t-AML among 63,359 epithelial OC [36].

For Cediranib, in general, the most important AEs associated to its administration consist of diarrhea, severe fatigue, severe neutropenia and febrile neutropenia, hypertension, GI

perforation, fistulae, arterial thromboembolism and posterior reversible encephalopathy syndrome (PRES). In Cediranib-treated patients who experienced diarrhea , most (84.8%) had CTCAE Grade 1 or 2 events. Diarrhea SAEs were infrequent (Cediranib concurrent/maintenance, 2.5%; Cediranib concurrent, 3.5%; chemotherapy+placebo, 2.6%). The incidence and severity of diarrhea were similar during the chemotherapy and maintenance phases in the Cediranib concurrent/maintenance arm and had intermittent characteristics. The onset of diarrhea was usually early, during the first treatment cycle, although it can occur or recur at any time during Cediranib treatment. Diarrhea was the most common AE leading to dose reductions, pauses and discontinuation of Cediranib. Patients tended not to start anti-diarrheal treatment immediately after the onset of diarrhea, contrary to the recommendation in the diarrhea management plan. Median exposure to Cediranib in the concurrent/maintenance arm was nearly 6 months longer in the subset of patients reporting use of anti-diarrhea l treatment compared to those who did not. Hypertension had an early onset but was successfully managed with standard anti-hypertensive therapy such as calcium channel blockers and angiotensin-converting enzyme inhibitors. Discontinuations, reductions or pauses of treatment due to hypertension were infrequent, with no evidence of hypertensive crisis or end organ damage.

In the combination Olaparib/Cediranib, as reported in the study by Liu J et al., the most frequent grade III or higher AEs in the Cediranib/Olaparib combination arm compared to control regimen consisted not only in hypertension but in diarrhea and fatigue also, suggesting an amplificatory effect caused by Cediranib [34].

The overall rate of grade 3/4 toxicity was higher for patients on combination therapy (70%) than on Olaparib alone (7%). Differentially occurring toxicities included fatigue (27% vs. 7%), diarrhea (23% vs. 0%), and hypertension (39% vs. 0%) [34].

1.2 Rationale for control groups and doses

As previously reported, the treatment of platinum resistant disease represents a struggle battle.

Paclitaxel is indicated as first-line (with cisplatin or carboplatin) and subsequent therapy for the treatment of OC [37]. Although this drug is approved for use in OC on a once every 3-week schedule, weekly administration of paclitaxel over 1 hour is a highly active and well-tolerated regimen that has been adopted for the treatment of relapsed OC. In studies of paclitaxel administered on the weekly schedule, overall tumor response rates have been reported ranging from 20% to 62% which are at least comparable and potentially higher than those achieved with the once every 3-week schedule in patients with [38]. In a Phase 3

clinical study comparing weekly versus once every 3-week paclitaxel in patients with epithelial cancer, there was no significant difference in overall response rate (35% vs. 37%, respectively; p = 0.89), median TTP (6.1 months vs. 8.1 months, respectively; p = 0.85) or median OS (13.6 months vs. 14.7 months, respectively; p = 0.98) [39]. The main toxicities associated with paclitaxel include myelosuppression and peripheral neuropathy. The DLT is myelosuppression, especially in heavily pretreated patients; however, other common AEs include allergic hypersensitivity reactions, alopecia, nausea, vomiting, diarrhea and mucositis [40]. Prophylactic pretreatment to decrease the risk of hypersensitivity is routine for patients receiving paclitaxel. This regimen involves dexamethasone (20 mg per os 12 hours before and 6 hours after paclitaxel, or a single 20 mg dose intravenously 30 minutes before paclitaxel) in conjunction with both H1 and H2 receptor antagonists (e.g., ranitidine and diphenhydramine) and antiemetic therapy. Recent evidence suggests that the conventional per os dosing regimen of dexamethasone may be more effective than the single-dose intravenous treatment. [41] Dexamethasone can be associated with short-term infections, and can lead to cumulative effects such as myopathy [42]. Peripheral neuropathy associated with paclitaxel therapy may be cumulative and may have a profound adverse effect on patient quality of life (QOL) [43]. The main toxicities of weekly paclitaxel were similar to those of paclitaxel administered every 3 weeks, although at a slightly lower frequency and severity, and dexamethasone-based premedication was also required. In a randomized clinical study directly comparing weekly versus once every 3-weeks administration schedules, there was a significantly lower incidence of Grade 3/4 neutropenia in the weekly treatment group (18% vs. 45%, respectively; $p < 0.001$). Moreover, weekly paclitaxel was associated with a significantly lower incidence of Grade 3 neuropathy (11% vs. 29%; $p < 0.001$) [39]. Additionally, in noncomparative clinical studies, weekly administration appeared to cause less neutropenia and peripheral neuropathy than historically reported frequencies with the standard schedule [44-46]. Thus, weekly paclitaxel may increase the probability of a patient achieving a beneficial tumor response with fewer AEs and cumulative neurotoxicity. For this reason the control group will be treated by weekly paclitaxel, regimen usually effective in this setting of patients.

The safety and efficacy of Olaparib has been demonstrated in the clinical programs using predominantly the capsule formulation (400 mg [8 capsules] bd as monotherapy). However, an improved tablet formulation has been developed. The dosage of 300 mg twice daily in tablet formulation was characterized by similar efficacy and tolerability compared to 400 mg twice daily in capsule formulation.. From the Phase 1 of the study of Liu J et al. the maximum tolerated dose was 200 mg bd daily in combination with Cediranib 30 mg once daily. Since in the study by Liu J et al., most of the AEs related to combined schedule derived from Cediranib administration, we decided to use the dosage of 600 mg tablet daily (300 mg bd daily). Considering the toxicities caused by 30 mg administration of Cediranib, the dosage

established is 20 mg, usually suggested when the drug is combined with other agents (see ICON 6 study that tested Cediranib concomitantly and after chemotherapy as maintenance) [21].

In the attempt to reduce toxicity, an intermittent schedule has been applied to other TKI, in particular Sunitinib[47]. Intermittent schedules allow a better dose intensity without impairing drug activity due to prolonged suspension for severe toxicity. Moreover, as the median half-life of Cediranib is quite long, but the cytokine release induced by VEFGR-1, VEGFR-2, VEGFR-3 is short-lasting, a 5 days out of 7 schedule may allow a better therapeutic index.
Thus, the identification of a less toxic and equally effective schedule of administration of this combined regimen represents an important issue.

Investigators should be familiar with the current Olaparib (AZD2281) and Cediranib (AZD2171) Investigator Brochures (IB).

1.3 Research hypothesis

As previously reported interesting results have been reported with the association of Cediranib and Olaparib in platinum sensitive disease.
However, no data are available about the clinical activity of this combination in a platinum resistant/refractory population.
Based on the available data, we hypothesize that the concomitant administration of these agents in platinum recurrent disease could give a therapeutic benefit.
Moreover, the use of alternative schedules should allow better compliance and adherence thanks to a better toxicity profile.

1.4 Rationale for conducting this study

In the last decades a lot of studies tried to individuate the best treatment option for platinum-resistant/refractory disease. However, results in terms of survival from these studies were inconclusive. Thus, the analysis of this setting of patients characterized by such a poor survival, represents an important issue.

PARP-inhibitors have been shown a strong activity in platinum-sensitive tumors overall in those patients affected by BRCA1-2 mutated OC.

Furthermore, another family of drugs that showed high activity in this neoplasia with an acceptable toxicity profile consists of anti-angiogenetic agents.

Preclinical and clinical studies showed a synergistic activity with concomitant use of Olaparib and Cediranib.

Clinical evidences showed that the combination of these drugs in platinum sensitive recurrent disease was effective with unexpected major activity in gBRCA wt tumors, probably due to a restored PARP inhibition, as previously reported.

Thus, the present study has the main purpose to test the combined use of Cediranib and Olaparib in recurrent or refractory disease. The control arm treatment will consist of weekly administration of Paclitaxel, one of the most effective regimens for the treatment of platinum resistant/refractory disease.

2. STUDY OBJECTIVES

2.1 Efficacy objectives

2.1.1 Primary objective

The efficacy primary objective is to compare Olaparib and Cediranib vs. Paclitaxel in terms of progression free survival (PFS) in platinum refractory or resistant recurrent OC.

2.1.2 Secondary objectives

Secondary efficacy objectives is the evaluation of treatment response as determined by RECIST 1.1, the prolongation of the time to second progression, overall survival and quality of life.

2.2 Safety objective

The primary objective for safety is to compare the safety of Olaparib and Cediranib as intermittent vs. continuous regimen in terms of number of evacuations per day.

Moreover, other study aims is to assess the safety and tolerability of combination of Olaparib and Cediranib vs. Paclitaxel as single agent chemotherapy.

2.3 Compliance objective

Another study aim is to assess the compliance to treatment.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a Phase II, randomised, multi-centre study to assess the efficacy of Cediranib-Olaparib combination in platinum refractory or resistant recurrence of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

All patients not previously tested for the presence of BRCA1-2 germline mutations, will undergo BRCA test.
However, both mutated and not mutated women will be included in the study protocol.
Weekly Paclitaxel will be used as comparator drug, due to its efficacy in platinum resistant/refractory disease.

Thus, patients will be randomised in a 1:1:1 ratio to the treatments as specified below:

- Paclitaxel 80 mg/mq every week (Arm A).
- Cediranib 20 mg/day + Olaparib 600 mg / day (i.e. 300 mg BD) given every day (Arm B).
- Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg / day (i.e. 300 mg BD) given 7 days per weeks (Arm C).

Randomisation will use a biased-coin minimization procedure having as stratification factors BRCA1-2 genes status (mutated vs. wilde-type vs. still unknown), prior chemotherapy (1-2 vs. $\geq$ 3 lines) and previous treatment with antiangiogenic drugs (yes vs. no).Treatment will be continued until progression, unacceptable toxicity, patient or physician decision to discontinue or death, for a maximum of 24 weeks (6 cycles) in the Paclitaxel arm.

Cross-over of the patients assigned to the control arm to the experimental arms, at disease progression, is not allowed.

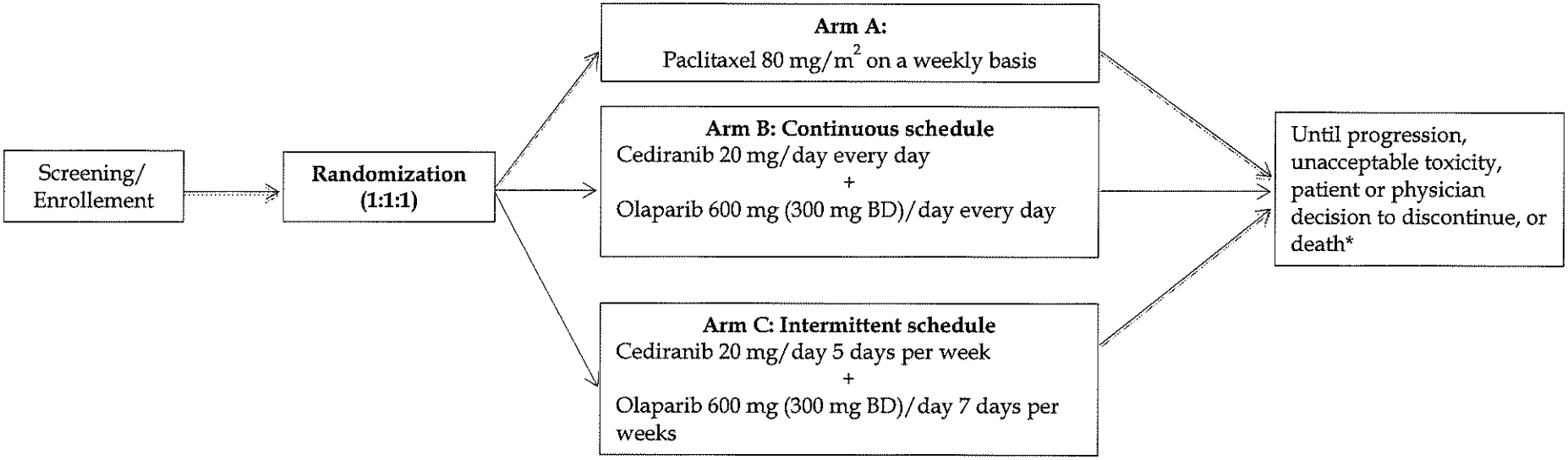
Progression will be established as the radiological disease progression according to RECIST 1.1 or as clinical progression in case radiological evaluation is not feasible due to clinical condition.

All patients should have RECIST assessments until documented evidence of radiological progression in accordance with RECIST 1.1, irrespective of treatment decisions (i.e RECIST follow up until progression even if a patient discontinues study treatment prior to progression and/or receives a subsequent therapy prior to progression).

Disease assessments will be scheduled every 8 weeks (+/- 1 week) from randomisation for all treatment duration and every 12 weeks (+/- 1 week) thereafter.

Once patients have been discontinued from study treatment, the investigator will be at liberty to further define the most appropriate anti-cancer treatment. Information on all subsequent anticancer treatments will be collected in the electronic case report form (eCRF).

Figure 1 Study flow-chart



*For Arm A (weekly Paclitaxel): maximum 24 weeks.

BD:twice daily

4. STUDY ENDPOINTS

4.1 Efficacy endpoints

4.1.1 Primary endpoint

The study primary endpoint is the PFS defined as the time from randomization to the date of first progression or death for any cause, whichever comes first.

Progression will be established as the radiological disease progression according to RECIST 1.1 or to clinical assessment in case radiological evaluation is not feasible due to clinical condition.

4.1.2 Secondary endpoints

Secondary endpoints are :

- Objective Response Rate (ORR), defined as the percentage of patients with an objective response as determined by RECIST 1.1
- PFS2 defined as time from randomization to second disease progression according to RECIST 1.1 or to clinical assessment, or death by any cause.
- Overall Survival (OS), defined in each patient as the time from randomization to the date of death for any cause.
- Quality of Life evaluated by the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire.

4.2 Safety endpoints

The primary endpoint for safety is the number of evacuations per day.

Secondary endpoints of safety are :

- the maximum toxicity grade experienced by each patient, for each toxicity, according to NCI-CTCAE v. 4.0;
- the number of patients experiencing grade 3-4 toxicity for each toxicity;
- type, frequency and nature of SAEs;
- patients with at least a SAE; patients with at least a SADR;
- patients with at least a SUSAR.
-

4.3 Compliance endpoints

The endpoints for compliance are :

- number of administered cycles
- reasons for discontinuation and treatment modification
- dose intensity

5. PATIENT SELECTION CRITERIA

5.1 Inclusion criteria

For inclusion in the study subjects should fulfill the following criteria:

1. Patients affected by pathologically confirmed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.

2. Relapsed/progressive disease within 6 months from last platinum-based chemotherapy (platinum resistant/refractory disease).

3. Any line of treatment (after the first).

4. Any "last" chemotherapy line, including Paclitaxel, that should have been administered at least 6 months before the study beginning.

5. Patients must be women $\geq$ 18 years of age.

6. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

   - Haemoglobin $\geq$ 10.0 g/dL and no blood transfusions in the 28 days prior to entry/randomisation

   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

   - White blood cells (WBC) $> 3 \times 10^9$/L

   - Platelet count $\geq 100 \times 10^9$/L

   - Total bilirubin $\leq$ 1.5 x institutional Upper Limit of Normal (ULN)

   - AST (SGOT)/ALT (SGPT) $\leq$ 2.5 x institutional Upper Limit of Normal unless liver metastases are present in which case it must be $\leq$ 5x ULN

   - Creatinine clearance estimated using the Cockcroft-Gault equation of $\geq$51 mL/min

Estimated creatinine clearance =[(140-age [years]) x weight (kg) (x F)] /[serum creatinine (mg/dL) x 72]; where F=0.85 for females.

7. ECOG performance status 0-1.

8. Patients must have a life expectancy ≥ 16 weeks.

9. Evidence of non-childbearing status for women of childbearing potential (negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1 or postmenopausal women. Postmenopausal status is defined as:
   - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
   - LH and FSH levels in the post-menopausal range for women under 50
   - Radiation-induced oophorectomy with last menses >1 year ago,
   - Chemotherapy-induced menopause with >1 year interval since last menses
   - Surgical sterilization (bilateral oophorectomy or hysterectomy)

10. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
11. At least one lesion (measurable as defined by RECIST 1.1) that can be accurately assessed by CT scan or MRI with Chest X-ray at baseline and follow up visits.

12. BRCA1-2 mutation status known. In case of BRCA status unknown, the BRCA test must be performed before the randomization or, if not feasible, within the end-of the study treatment.

13. Provision of informed consent prior to any study specific procedures. In case of patients unable to give written informed consent, is necessary to have the subject or legal representative sign, but in any case a witness must be present and sign and date with the person conducting informed consent.

5.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled

1. Any previous treatment with a PARP inhibitor, including Olaparib.

2. Prior treatment with Cediranib (previous bevacizumab or other antiangiogenic drug are allowed).

3. Previous progression to weekly Paclitaxel.

4. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥ 5 years.

5. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment with study drug.

6. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting Olaparib is 2 weeks.

7. Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting Olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

8. Persistent toxicities (>=CTCAE grade 2) with the exception of alopecia, caused by previous cancer therapy.

9. Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.

10. Greater than +1 proteinuria on two consecutive dipsticks taken no less than 1 week apart unless urinary protein < 1.5g in a 24 hr period or urine protein/creatinine ratio < 1.5

11. A history of poorly controlled hypertension or resting blood pressure >150/100 mmHg in the presence or absence of a stable regimen of anti-hypertensive therapy (measurements will be made after the patient has been resting supine for a minimum of 5 minutes. Two or more readings should be taken at 2-minute intervals and averaged.

If the first two diastolic readings differ by more than 5 mmHg, then an additional reading should be obtained and averaged).

12. Blood transfusions within 1 month prior to study start

13. Features suggestive of MDS or AML on peripheral blood smear.

14. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 28 days prior to treatment.

15. Major surgery within 4 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

16. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression (untreated and unstable for at least 28 days prior to study entry), superior vena cava syndrome, extensive bilateral lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent.

17. Patients unable to swallow medications and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

18. Breast feeding women.

19. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy.

20. Patients with known active hepatic disease (i.e., Hepatitis B or C).

21. Patients with a known hypersensitivity to Olaparib, Cediranib or any of the excipients of the product.

22. Patients with a known hypersensitivity to Paclitaxel.

23. Patients with uncontrolled seizures.

24. History of abdominal fistula or gastrointestinal perforation.

25. Prior gastrectomy.

Procedures for withdrawal of incorrectly enrolled subjects (see Section 6.12).

6. STUDY CONDUCT

6.1 Restrictions during the study

Contraception

Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

- Condom with spermicide

and one of the following:

- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) + male condom with spermicide. Provided coils are copper-banded

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide

- Norelgestromin/ethinyl estradiol (EE) transdermal system + male condom with spermicide

- Intravaginal device + male condom with spermicide (eg, EE and etonogestrel)

- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill

Food intake restrictions

Patients should take Cediranib no sooner than 1 hour after food. They should then refrain from eating for a further 2 hours due to potential effect of food on absorption as reported in Cediranib IB. Olaparib tablets can be taken with or without food.

It is not recommended to consume grapefruit juice while on Olaparib therapy.

Other Concomitant treatment

- No other chemotherapy, hormonal therapy (HRT is acceptable) or other novel agent is to be permitted during the course of the study for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment, as per exclusion criteria above). Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present (see Section 7.7.3).

- Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with Olaparib/Cediranib combination are unknown.

- Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section **Errore. L'origine riferimento non è stata trovata.**) from the time they enter the screening period until 30 days after the last dose of study medication. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of Olaparib is CYP3A4 and consequently, this restriction is required to ensure patient safety.

- Caution should be exercised in the concomitant use of any medication that may

markedly affect renal function (e.g. vancomycin, amphotericin, ibuprofen, pentamidine). Such medications may, however, be used with caution if deemed essential for treatment of a particular infection or continued if patients are using them prior to commencing the study with no effect on renal function demonstrable on blood or urine testing.

- Caution should be exercised in concomitant use of any medication that may affect hepatic CYP450 drug metabolizing activity by way of enzyme induction (e.g., phenytoin) or inhibition (e.g., ketoconazole, ritonavir, erythromycin) within 2 weeks of the first dose of Cediranib and throughout the study period.

- Patients who require oral anticoagulants (coumadin, warfarin) are eligible, provided there is increased vigilance with respect to monitoring INR. If medically appropriate and treatment available, consider switching to low molecular weight heparin.

- Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator.

6.2 Subject enrollment and randomization

6.2.1 Procedures for randomization

Investigator(s) should keep a record of the patient screening log and of patients who entered pre-study screening.

The investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed. For patients with unknown BRCA status, the BRCA test will be performed only after informed consent signature. The study informed consent reported details also about the BRCA test that to be performed during the Screening Part 1 visit.

2. Register the patient through the system.

3. Determine patient eligibility.

4. Randomize the patient through the system. In case of BRCA status unknown, the BRCA test must be performed before the randomization or, if not feasible, within the end-of the study treatment.

6.3 Procedures for handling subjects incorrectly enrolled or randomized

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study. Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the Sponsor immediately, and a discussion should occur between the Sponsor and the investigator regarding whether to continue or discontinue the patient from treatment. The Sponsor must ensure all decisions are appropriately documented. The withdrawals after randomization should be reported in the eCRF.

6.4 Tumor assessments

Baseline assessment will be performed no more than 28 days prior to study treatment start and as close as possible to study treatment start.

Following the baseline assessment (at screening), subsequent tumor assessments according to RECIST 1.1 should be performed at the end of every 8 weeks (+/- 1 week) from randomisation for 48 weeks and every 12 weeks (+/- 1 week) thereafter.

All patients should have RECIST assessments until documented evidence of radiological progression in accordance with RECIST 1.1, irrespective of treatment decisions (i.e RECIST follow up until progression, even if a patient discontinues study treatment prior to progression and/or receives a subsequent therapy prior to progression).

At baseline, the imaging modalities used for RECIST assessment will be CT (MRI where CT is contraindicated) scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease.

Follow-up CT or MRI assessments will cover chest (in those patients with disease in the chest or upper abdomen lymphadenopathy at baseline), abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumour burden used at baseline must be used at each subsequent follow-up assessment.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit ± 1 week window interval and the patient has not progressed, every

attempt should be made to perform the subsequent scans at their scheduled time points.

Patients will be evaluated until radiological disease progression by RECIST 1.1 as per the study schedule and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

The RECIST 1.1 guidelines for measurable, non-measurable, target and non- target lesions and the objective tumour response criteria (complete response "CR", partial response "PR", stable disease "SD" or progression of disease "PD") are presented in Appendix 3.

Although CA-125 is measured in this study it will not be directly used for assessing objective response or progression and patients should be continued on treatment until radiological disease progression as defined by RECIST 1.1. CA-125 will be tested at day 1 (if not performed at screening) and every month thereafter until serological disease progression as per GCIG CA-125 criteria.

If the investigator is in doubt whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Following progression, patients should continue to be followed up for survival every 12 weeks as outlined in the Study Schedule (Appendix 1). It is important to follow the assessment schedules as closely as possible.

6.5 Laboratory assessments

Blood and urine samples for determination of clinical chemistry (sodium, potassium, calcium, fasting glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]), haematology (haemoglobin, platelets, mean cell volume [MCV], white blood cells [WBC], absolute neutrophil count, absolute lymphocyte count), coagulation (activated partial thromboblastin time [APTT] and international normalised ratio

[INR]) should be performed at screening, on day 1 (if the exams are performed more than 7 days before treatment start), weekly for the first cycle, then every four weeks up to 52 weeks, then every 12 weeks until the end of study treatment.

In case of BRCA status unknown at enrollment, the BRCA test must be performed. Blood sample for BRCA evaluation must be taken before the randomization.

Urinalysis (by dipstick or 24-hour urine collection if clinically indicated) should be taken at screening, day 1, and then monthly, as indicated in the Study Schedule (Appendix 1).

Patients taking warfarin may participate in this study; however, it is recommended to carefully monitor prothrombin time (INR and APTT) at least once per week for the first month, then monthly if the INR is stable.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

6.6 Physical examination

A complete physical examination should be performed at screening and then every 4 weeks, as reported in the Study Schedule (Appendix 1), and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, muscle-skeletal (including spine and extremities) and neurological systems.

6.7 ECG

ECGs are required at screening within 7 days prior to starting study treatment and as clinically indicated afterwards. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

6.7.1 Resting 12-lead ECG

At screening, mean QTc with Bazetts correction must be <470msec. Bazetts correction formula is: $QTc = QT/\sqrt{RR}$.

6.8 Vital signs and performance status

Height will be assessed for determination of Paclitaxel dose.

Weight will be assessed at screening according to the Study Schedule (Appendix 1) and as clinically indicated at any other time. ECOG performance status will be evaluated at screening, at day 1, monthly, at discontinuation of treatment and during follow-up.

6.8.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured preferably using a semi automatic BP recording device with an appropriate cuff size after 10 minutes rest on a bed. Blood pressure and pulse will be measured at baseline and at each visit (see Study Schedule - Appendix 1).

The date of collection and measurement will be recorded on the appropriate eCRF.

Moreover, patients should measure and register blood pressure values in the patient diary daily.

6.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at baseline and as clinically indicated afterwards (see Study Schedule - Appendix 1).

6.9 Serum or urine pregnancy test

Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential, one within 28 days prior to the start of study treatment and the other on Day 1 of the study, prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

6.10 Bone marrow or blood cytogenetic analysis

Bone marrow or blood cytogenetic analysis may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 7.6. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to Coordinator Safety Board for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

6.11 Patient reported outcomes (PRO)

FACT-O will be administered in this study in order to assess QOL among different treatment regimens at baseline and then every 4 weeks for 6 months or until treatment discontinuation, whichever comes first.

The FACT-O is composed of the following sub-scales: physical, social/family, emotional, and functional well-being as well as the additional concerns scales, consisting of specific OC symptoms. The main endpoint for health- related quality of life analysis is the Trial Outcome Index (TOI), an established single targeted index derived from the FACT-O questionnaire and it is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms and AEs. The TOI is composed of the following scales of the FACT- O: physical and functional well-being and additional concerns.

6.12 Withdrawal from study

Reasons for withdrawal from the study will be:

• Voluntary withdrawal by the patient, who is at any time free to discontinue their participation in the study, without prejudice to further treatment.

• Incorrectly enrolled patients, i.e. the patient does not meet the required inclusion/exclusion criteria for the study. This option is only applicable to patients not randomised into the study (i.e. screen failures identified prior to randomisation).

• Patient lost to follow-up.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The investigator will follow up AEs outside of the clinical study.

Patient is considered lost to follow-up when any of the following attempts of contact are failed and one unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations, was performed.

6.13 Follow-up procedures

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 7.9). The assessments are detailed in the Study Schedule (Appendix 1).

In case of objective radiological disease progression according to RECIST (see Appendix 3), patient should be discontinued from study treatment unless in the investigator's opinion she is benefiting from treatment. These patients will continue on treatment and will be followed

safety assessment with the same frequency as the visits, unless more frequent testing is clinically indicated. Drug accountability should continue to be performed until the patient stops study treatment completely.

A follow-up visit should be conducted 30 days after the last dose of study treatment. Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have occurred during the defined 30-day follow-up period must be followed-up. Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30 day follow up visit are detailed in the Study Schedule (Appendix 1). Any SAE or non-serious adverse event, that is ongoing at Discontinuation Visit , must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

Patients will be assessed every 12 weeks for a second progression (using the patients status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to objective radiological (RECIST criteria), clinical progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.Assessments for survival should be made every 12 weeks. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final OS analysis. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries.

Patients will be followed up as per Study Schedule (Appendix 1) to the point of the final analysis. At this point investigators will be notified that no further data collection for the study is required. Monitoring and recording of SAEs will continue as per Section 8.

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify it to the study

Safety desk.

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7. TREATMENTS

7.1 Identity of investigational product(s)

The Pharmaceutical Development R&D Supply Chain of AstraZeneca will supply both Olaparib and Cediranib to the investigators as oval tablets for Olaparib and round tablets for Cediranib.

Investigational product	Dosage form and strength
Olaparib	100 mg and 150 mg tablets
Cediranib	20 mg and 15 mg tablets

Descriptive information for Olaparib and Cediranib can be found in the Investigator's Brochure

7.2 Doses and treatment regimens

Paclitaxel (Arm A)
Commercial Paclitaxel will be utilized in this study. Paclitaxel will be administered according to the prescribing information on Days 1, 8, 15 and 22 of each 4 weeks cycle as an IV infusion at a starting dose of 80 mg/m^2 in 1 hour total infusion. For an individual patient, the dose of Paclitaxel may be reduced or interrupted as appropriate based on treatment modifications as follows.

Table 1 Paclitaxel Dose Levels

Dose Level	Dose	Schedule
1	80 mg/m^2	Days 1, 8, 15, and 22 every 4 weeks
-1	65 mg/m^2	
-2	50 mg/m^2	

The appropriate dose to be administered to each patient will be calculated at the beginning of each 4 weeks cycle based on their BSA.
Patients should be pretreated with corticosteroids, diphenhydramine and/or H2 antagonists according to institutional standards.
The administration of Paclitaxel at the beginning of every cycle will have a ± 3-day window unless unacceptable toxicity occurs.
Refer to the Paclitaxel prescribing information for additional information.

Olaparib and Cediranib (Arm B and Arm C)

Arm B: Olaparib 600 mg/day (300 mg tablets, consisting of 2 150 mg tablets administered twice/day, for a total of 4 150 mg tablets/day) + Cediranib 20 mg /day (one 20 mg tablet/day) both administered all days without stop. (Continuous schedule).

Patients should take Olaparib two times per day, in the morning and in the afternoon. Olaparib tablets can be taken with or without food. In any case, when patient take Olaparib concomitantly with Cediranib, they should take Cediranib and Olaparib no sooner than 1 hour after food. They should then refrain from eating for a further 2 hours due to potential effect of food on absorption as reported in Cediranib IB.

The tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

Arm C: Olaparib 600 mg/day (300 mg tablets, consisting of 2 150 mg tablets administered twice/day, for a total of 4 150 mg tablets/day) 7 days per week + Cediranib 20 mg /day (one 20 mg tablet/day) 5 days per week. (Intermittent schedule). Patients should take Olaparib two times per day, in the morning and in the afternoon. Olaparib tablets can be taken with or without food. In any case, when patient take Olaparib concomitantly with Cediranib, they should take Cediranib and Olaparib no sooner than 1 hour after food. They should then refrain

from eating for a further 2 hours due to potential effect of food on absorption as reported in Cediranib IB.

The tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

Table 2 Olaparib Dose Levels

Dose Level	Dose	Schedule
1	600 mg/day (300 mg BD)	7 days per week in both arm
-1	500 mg/day (250 mg BD)*	
-2	400 mg/day (200 mg BD)**	

BD: twice daily

*** The Olaparib 250 mg dose reduction would be carried out by giving one 150 mg tablet +one 100 mg tablet.**

**** The Olaparib 200 mg dose reduction would be carried out by giving two 100 mg tablets.**

Table 3 Cediranib Dose Levels

Dose Level	Dose	Schedule
1	20 mg/day	Every day/7 days in Arm B Every day/5 days per week in Arm C
-1	15 mg/day	

7.3 Labelling

Drugs (Olaparib and Cediranib) furniture will be provided in bulk by AstraZeneca. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines by internal pharmacy of Coordinating site (Istituto Europeo di Oncologia, Milano). The labels will fulfill GMP Annex 13 requirements for labelling. The labelling of the drugs will be performed by the pharmacy of Istituto Europeo di Oncologia, Milano.

Indeed, each bottle of both Olaparib and Cediranib will have an investigational product label permanently affixed to the outside, stating that the material is for clinical trial/investigational use only and should be kept out of reach and sight of children. The label will include the dosing instructions and a space for the randomization code (trial code) to be completed at the time of dispensing. All these procedures will be performed by the internal pharmacy of IEO.

AstraZeneca will provide different forms of tablets for dose reductions (100 and 150 mg for Olaparib and 20 and 15 mg for Cediranib).

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the Investigator's Brochure specify the appropriate storage.

7.5 Management of toxicity of paclitaxel

Doses of Paclitaxel should be adjusted for AEs throughout the study. A patient may have up to 2 dose reductions of Paclitaxel (Table 1).
When a dose reduction is required because of an AE, no subsequent dose re-escalation will be permitted for that patient for the duration of study treatment. In addition to the dose modification guidance provided below, please refer to the Paclitaxel local prescribing information for additional dosing and safety guidance for its administration.

Patients who experience severe hypersensitivity reactions to Paclitaxel should not receive further administration of the drug, unless not appropriately pre-medicated.
If the patient experiences a Paclitaxel-related infusion reaction that cannot be managed according to the Paclitaxel prescribing information, the patient should permanently discontinuethe treatment.

For recommended Paclitaxel dose modifications, based on the occurrence of treatment-related AEs, see Table 4.

Table 4 Management of Paclitaxel toxicity

Toxicity	Intervention
• ANC $\leq 0.8 \times 10^9$/L and/or platelet $\leq 50 \times 10^9$/L • Any motor or sensory neuropathy ≥ Grade 2 • Any renal AE ≥ Grade 2 • Liver AE ≥ Grade 3 (manifested as elevations in ALT, AST, AP or bilirubin) • Any other AE ≥ Grade 3	Hold Paclitaxel until Grade ≤ 1 or Baseline severity and then resume scheduled Paclitaxel dosing • If AE resolved in ≤ 14 days, then resume scheduled weekly Paclitaxel treatments at a reduced dose. • If AE is not resolved in > 14 reduce or discontinue Paclitaxel If unacceptable Paclitaxel-related AE reoccurs after initial dose reduction to 65 mg/m^2, subsequent scheduled weekly Paclitaxel treatments should be administered at a reduced dose of 50 mg/m^2

7.6 Management of toxicity of Olaparib and Cediranib combination

Any toxicity observed during the course of the study could be managed by interruption and/ or dose reduction, if deemed appropriate by the Investigator.

Repeated dose interruptions are allowed as required. If the interruption is longer than 14 days (continuous period), the Sponsor must be informed. In any case the maximum time of interruption allowed is 4 weeks.

Treatment must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (current version) grade 1 or less.

Where toxicity reoccurs following re-challenge and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue treatment.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to its administration.

Myelosuppression will be most likely related to Olaparib administration. Thus, its management should be as follows.

Management of anaemia

Adverse events of anaemia CTCAE grade 1 or 2 (Haemoglobin (Hb) $\geq$ 8 g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of Olaparib or change in dose, taking into account previous history of anaemia. Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases management of anaemia may require blood transfusions.

However, if a patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, Olaparib should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the patient should be managed appropriately.

Olaparib can be restarted at the same dose if Hb has recovered to $\geq$ 10 g/dl. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require dose reductions of Olaparib.

If a patient has been treated for anaemia with multiple blood transfusions without interruptions of Olaparib and becomes blood transfusion dependant–as judged by investigator, Olaparib should be permanently discontinued.

Management of neutropenia and leukopenia

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of Olaparib if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended.

If a patient develops febrile neutropenia, the treatment with Olaparib should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTC AE grade $\geq$1 (ANC $\geq$ 1.5 x 10^9/L). Growth factor

support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require dose reductions of Olaparib according to Table 2.

Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator.
If a patient develops thrombocytopenia CTCAE grade 3 or worse, Olaparib should be interrupted for a maximum of 4 weeks.
In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.
Even if in most of the cases myelosuppression will be due to Olaparib administration, it must be remembered that trombocytopenia, of CTCAE grade 1 or 2 in the majority of cases has been seen during monotherapy and combination Cediranib treatment.
Moreover, although the effect of short treatment breaks of Cediranib on platelet count recovery has not been studied, it is possible that a short break of a few days may help in the situation of CTCAE grade 3 or grade 4 or prolonged thrombocytopenia.
For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), see the following paragraph.

Management of prolonged haematological toxicities while on study treatment

Haematological toxicities will be mainly due to Olaparib.

If a patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in Olaparib due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in Olaparib due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in Olaparib due to CTC grade 3 or worse thrombocytopenia (platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x haematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to

haematologist for further investigations and considered for Cediranib reduction/interruption also. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE; full reports must be provided by the investigator to Sponsor Safety desk. Study treatment should be discontinued if diagnosis of MDS is confirmed.

Table 5 Haematologic toxicity: CTCAE and management in Cediranib/Olaparib combination

Hematologic toxicity	Cediranib	Olaparib
• CTCAE gr 1-2	No change	Investigator judgment to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
• CTCAE gr 3-4	No change	Interruption until toxicity recovery to CTCAE gr 1 or better for a maximum of 4 weeks. If repeated CTCAE gr 3-4 occurrence, Olaparib dose reduction to 250 mg bd as a first step and 200 mg bd as a second step

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in Olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then Olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Sponsor.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

All drugs should be stopped before surgery and re-started after wound has healed following recovery, with an appropriate timing for Cediranib.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with Olaparib treatment.

In study D0810C00019[47] nausea was reported in 71% of the Olaparib treated patients and 36% in the placebo treated patients andvomiting was reported in 34% of the Olaparib treated patients and 14% in the placebo treated patients.

They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles. In the study by Liu J *et al.* [34], there was not a statistically significant difference in terms of toxicity in the group of patients who underwent to Cediranib/Olaparib combination. Thus, no routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. In case of persistent nausea a dose reduction of Olaparib must be considered according to Table 2.

Management of diarrhea

Cediranib is associated with diarrhea and therefore action should be taken to minimize its effects as soon as symptoms develop. Scientific evidences showed that Cediranib/Olaparib combination is associated with higher incidence of diarrhea compared to Olaparib treatment alone. The recommendations for diarrhea management have been established on guidelines from the American Society of Clinical Oncology on the basis of the last version of NCI CTCAE (modified NCI CTCAE, Version 4.03 - see Table 6).

Table 6 Management of diarrhea

• CTCAE gr 1	Increase of < 4 stools per day over Baseline; mild increase in ostomy output compared to Baseline
• CTCAE gr 2	Increase of 4-6 stools per day over Baseline; moderate increase in ostomy output compared to Baseline
• CTCAE gr 1-2 complicated	Definition as above (Grade 1/2) with the following complicating signs/symptoms: • Moderate to severe cramping • Grade ≥ 2 nausea/vomiting • Decreased performance status • Fever • Sepsis • Neutropenia • Frank bleeding • Dehydration • Unresolved diarrhea after 48 hours of treatment with loperamide (including high-dose administration) and initiation of second-line treatment
• CTCAE gr 3	Increase of ≥ 7 stools per day over Baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to Baseline; limiting self-care activities of daily living
• CTCAE gr 4	Life threatening consequences; urgent intervention indicated

These guidelines recommend that treatment induced diarrhea should be carefully monitored and treated aggressively to ensure that severe complications are avoided and that chemotherapy regimens are not delayed (Benson *et al.*) [47].

Initial management of diarrhea

- Patients should be made aware that they are likely to experience diarrhea
- Patients should be given loperamide to take home with them
- If diarrhea occurs patients should immediately start loperamide after the first episode (4mg initially then 2mg every 2 hrs) and continue to take it until they have been free from diarrhea for at least 12 hrs
- Patients should be encouraged to drink plenty of fluids

- Patients should seek advice early, from their physician or study nurse, if

  – Grade 1 or 2 diarrhea persists for over 24hrs despite treatment with loperamide

  – Grade 3 diarrhea develops

  – Any grade of diarrhea associated with vomiting, marked abdominal distension or inability to take oral fluids develops

Management of persistent (>24h) diarrhea despite loperamide

Patients should be advised to hold the Cediranib study tablets for 1-2 days and care should be taken to prevent dehydration.

Following evaluation, consider antibiotics (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic or has a fever.

Consider infectious causes and etiologies such as C-difficile/viral gastroenteritis.

Management of persistent (>48h) diarrhea despite loperamide

The physician or study nurse should see patients in this situation. Hospitalisation and IV fluids may be needed.

Consider infectious causes and etiologies such as C.difficile/viral gastroenteritis.

Consider antibiotics (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic or has a fever.

Octreotide (Sandostatin) may be considered.

In case of Grade 3/4 diarrhea refractory to oral anti-diarrhea medication, all treatment will be held. If ≥ CTCAE Grade 3 diarrhea persists after 2 weeks, both Cediranib/Olaparib should be discontinued. If the toxicity resolves to ≤ CTCAE Grade 1, then Cediranib/Olaparib will be restarted and the dose reduced according to local practice. If ≥ CTCAE Grade 3 diarrhea recurs Cediranib/Olaparib should be discontinued.

Fatigue management

Fatigue experienced by patients taking Olaparib/Cediranib may be rapid in onset. During appointments patients fatigue levels should be discussed.

Patients should seek medical advice early if Grade 2 fatigue develops (moderate fatigue causing difficulty performing some activities of daily living).

Patients should be advised to take short treatment breaks of the study tablets (initially 2-3 days-or longer-up to a maximum of 14 days), in order to help relieve this symptom.

Care should be taken to ensure that the patients' nutritional status is optimised.

Patients should be encouraged to drink plenty of fluids (1.5 L/day- sips).

Consideration should also be given to other causes e.g. depression, insomnia, thyroid function, diarrhea /dehydration, anaemia, drug use e.g. CNS depressants and anxiolytics or adrenal function.

Patients should be encouraged to manage fatigue by alternating periods of rest with frequent light exercise, which may improve the symptoms in some cases.

Patients should restart treatment when symptoms have improved.

Reversible Posterior Leucoencephalopathy Syndrome (RPLS)

Cases of Magnetic Resonance Imaging (MRI)-documented RPLS have been reported in patients receiving Cediranib. RPLS is a rare syndrome affecting vascular endothelial cells in the brain that may lead to capillary leak and oedema, and was first described in 1996 (Hinchley et al 1996). It has been associated with a number of conditions, including renal failure, hypertension, fluid retention, and the use of cytotoxic or immunosuppressive drugs. It has also been reported in association with the use of VEGF inhibitors including bevacizumab sunitinib and sorafenib. RPLS can present in a variety of non-specific ways, including headache, seizures, lethargy, confusion, blindness and other visual and neurological disturbances. Hypertension may be present, but is not necessary for the diagnosis of RPLS. MRI is the most sensitive imaging modality for detection of RPLS and is recommended in suspected cases to confirm the diagnosis. RPLS is reversible upon removal of any possible precipitating factors and control of hypertension. Active management of hypertension according to the hypertension management guidelines (see the paragraph on Hypertension) may be expected to reduce the incidence of RPLS. However, if any case of RPLS occurs that is confirmed by imaging (CT or MRI), Cediranib should be immediately discontinued, in addition to any other measures to alleviate symptoms and control blood pressure. Investigator should consider the interruption of both drugs.

CNS bleeding

Patients should be monitored for signs and symptoms of CNS bleeding, and the study treatments discontinued in case of intracranial bleeding of any grade. Patients with untreated CNS metastases were routinely excluded from clinical trials with antiangiogenetic agents, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patients has not been prospectively evaluated.

Hypertension

Since the use of antiangiogenetic drugs (such as Cediranib) showed to be frequently associated to hypertensive disorders, patients must be closely monitored on study for the development or worsening of hypertension. Blood pressure measurements should occur after the patient has been in a resting position for ≥5 minutes. If the initial BP reading is ≥140 mmHg systolic and/or ≥90 mmHg diastolic pressures, the result should be verified with a repeat measurement. If hypertension occurs, combination treatment should be managed as described in

Table 7.

Table 7 Hypertension: CTCAE and management in Cediranib/Olaparib combination

Toxicity	Cediranib	Olaparib
• CTCAE gr 1 (Systolic 120-139 mmHg or diastolic 80-89 mmHg)	Consider increased BP monitoring	No change
• CTCAE gr 2 (Stage 1 Hypertension: systolic 140-159 mmHg or diastolic 90-99 mmHg); medical intervention indicated; recurrent or persistent > 24 hrs); symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously WNL; monotherapy indicated	Start/ add long acting DHP CCB. Gradually increase dose to control BP up to maximum dose. If partial or no control and still moderate hypertension, add an additional drug and increase dose until BP control up to maximum dose. Restart Cediranib at one lower dose level (when controlled). First occurrence: Continue Cediranib at full dose or decrease dose by one level Second occurrence: Decrease Cediranib dose by one level	No change
• CTCAE gr 3 (Stage 2 hypertension: systolic > 160 mmHg or diastolic > 100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	If asymptomatic, hold Cediranib and start immediate antihypertensive therapy with 2 drug combination including at least a DHP CCB. Increase dose until BP control up to maximum dose of both agents. If control to mild hypertension range, restart Cediranib at one dose level lower. If partial or no BP control, add another drug and increase dose until BP control up to maximum dose. If partial or no control, stop Cediranib. If symptomatic: stop Cediranib, hospitalize with aggressive IV therapy as per hypertensive crisis management. First occurrence: hold Cediranib until diastolic BP < 100 mmHg and	No change Evaluate discontinuation of both drugs

	decrease dose by one level Second occurrence: hold Cediranib until diastolic BP < 100 mmHg and stop Cediranib permanently	
• CTCAE gr 4 Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit, hypertensive crisis); urgent intervention indicated	Stop Cediranib, hospitalize with aggressive IV therapy as per hypertensive crisis management. Stop Cediranib permanently	Evaluate discontinuation of both drugs

Thrombo-embolism

Arterial thromboembolism

If a patient experiences any grade of arterial thromboembolism during the study treatment period, treatment should be discontinued permanently.

Venous thromboembolism

Patients experiencing a grade 4 thrombosis must discontinue treatment permanently. If a patient experiences a grade 3 venous thromboembolism, treatment must be withheld for 3 weeks. Treatment may be resumed during the period of therapeutic-dose anticoagulant therapy. Asymptomatic venous emboli and thromboses detected during the study as an incidental finding on routine CT scans should be considered on a case by case by the investigator whether the treatment may be continued or not for a patient.

Note that pulmonary emboli are considered as venous in origin.

Management of proteinuria

During treatment if a patient has two consecutive two plus (++) urine protein dipstick measurements, or one three plus (+++) or greater measurement, a 24-hour urine specimen or urine protein/creatinine ratio sample should be collected. A urine protein/creatinine ratio of 0.15 (urine protein and urine creatinine expressed in mg/dL) approximates a 24-hour urine protein of 150 mg/24 hours or 0.15g/24 hours, which is the upper limit of normal (Rodby *et al.* 1995, Schwab *et al.* 1987, Wingo and Clapp 2000). If 24-hour proteinuria or urine protein creatinine ratio is classified as CTCAE grade 3 see Table 8. If nephrotic syndrome occurs, Cediranib should be permanently discontinued.

Table 8 Proteinuria: CTCAE and management in Cediranib/Olaparib combination

Toxicity	Cediranib	Olaparib
• CTCAE gr 1 (stick 1+; urinary protein <1.0 g/24 hrs; urine protein/creatinine ratio of 0,15-0,10 mg/dL)	No change	No change
• CTCAE gr 2 (stick 2+/3+; urinary protein 1.0 - 3.4 g/24 hrs; urine protein/creatinine ratio of > 1,0-3,5 g/dL)	Suspend Cediranib for urine protein level ≥ 2 g/24 hrs and resume when proteinuria is < 2 g/24 hours For 2+ dipstick: may administer Cediranib; obtain 24-hour urine prior to next Cediranib dose For 3+ dipstick: obtain 24-hour urine prior to Cediranib administration	No change
• CTCAE gr 3 (stick 4+; urinary protein >3.5 g/24 hrs; urine protein/creatinine ratio of > 3,5 g/dL)	Suspend Cediranib. Resume when proteinuria is < 2 g/24 hrs, as determined by 24-hrs urine collection <2.0 g.	No change
• CTCAE gr 4 Nephrotic syndrome	Permanently discontinue Cediranib	Evaluate discontinuation of both drugs

Management of abnormal thyroid function

Cediranib therapy has been associated with increases in TSH. In the majority of patients this has not resulted in reductions in either total triiodothyronine (T3) or free thyroxine (T4) below the lower limit of the normal range, but clinical hypothyroidism has been reported in a small number of patients. Patients have responded to replacement therapy without the need for stopping or reducing the dose of Cediranib.

Replacement levothyroxine should be given when clinically indicated to normalise the thyroxine level to within the normal range, and before the patient becomes clinically symptomatic. Replacement levothyroxine therapy may also be considered in patients with TSH increases (and thyroxine levels within the normal range), together with adverse events and symptoms suggestive of incipient hypothyroidism. Thyroid function should be monitored frequently and the dose of levothyroxine should be titrated as required.

Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation between 31 and 50 ml/min) for any reason during the course of the study: the dose of Olaparib should be reduced to 200 mg/day.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended Olaparib to be discontinued.

Thus, the experimental regimens should be permanently discontinued in patients experiencing any of the following events:

- Reversible Posterior Leucoencephalopathy Syndrome (RPLS) – consider temporarily/permanently discontinuation of both drugs; Olaparib could be considered for continuation.
- Grade 3/4 hemorrhagic/bleeding events – consider temporarily/permanently discontinuation of both drugs, in case of resolution Olaparib could be restarted.
- Any grade of CNS bleeding – consider temporarily/permanently discontinuation of both drugs.
- Any grade of arterial thromboembolism (note pulmonary emboli are considered venous thromboemboli) – permanently discontinuation of Cediranib; Olaparib administration could be continued.
- Grade 4 venous thromboembolism – permanently discontinuation of Cediranib; Olaparib administration could be continued with adequate anti-thrombotic prophylaxis.
- Grade 4 hypertension (hypertensive crisis) – permanently discontinuation of Cediranib; Olaparib administration could be continued.
- Nephrotic syndrome – permanently discontinuation of Cediranib; Olaparib administration could be continued.
- Grade 3/4 left ventricular dysfunction (CHF) – consider temporarily/permanently discontinuation of both drugs.
- Any grade of gastrointestinal perforation – consider temporarily/permanently discontinuation of both drugs, in case of resolution Olaparib could be restarted.
- Any grade of tracheo-esophageal fistula – consider temporarily/permanently discontinuation of both drugs, in case of resolution Olaparib could be restarted.
- Grade 4 non-gastrointestinal fistula – consider temporarily/permanently discontinuation of both drugs, in case of resolution Olaparib could be restarted.
- Any grade of hypersensitivity/allergic reactions to Cediranib/Olaparib administration – permanently discontinuation of drug responsible of allergy.
- Bone marrow findings consistent with MDS/ AML – consider temporarily/permanently discontinuation of both drugs, Cediranib could be restarted.
- Severe renal impairment – consider permanently discontinuation of both drugs.

The maximum time of interruption allowed will consist of 4 weeks.

7.7 Concomitant and other treatments

The use of any natural/herbal products or other traditional remedies should be discouraged

7.7.1 Medications that may not be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with Olaparib are unknown.

7.7.2 Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with Olaparib.

If there is no suitable alternative concomitant medication then the dose of Olaparib should be reduced for the period of concomitant administration. The dose reduction of Olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of Olaparib to 100 mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of Olaparib to 200mg bd for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards.
- After the washout of the inhibitor is complete, the Olaparib dose can be re-escalated.

Strong or Moderate CYP3A inducers

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with Olaparib.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of Olaparib.

If a patient requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of Olaparib.

P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (eg clarithromycin, itraconazole, erythromycin) may increase exposure to Olaparib. Caution should therefore be observed.

Effect of Olaparib on other drugs

Based on limited *in vitro* data, Olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited *in vitro* data, Olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

The efficacy of hormonal contraceptives may be reduced if co administered with Olaparib.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

In vitro studies suggested that Cytochrome P450 (CYP) enzymes were not significantly involved in the production of the principle human metabolites of Cediranib, therefore co-administration of known inhibitors or inducers of hepatic CYP enzymes would not be expected to have significant effects on the clearance of Cediranib. However, since potent inhibitors or inducers of CYP enzymes can also affect drug disposition by interaction with transporter proteins and Phase II metabolism, 2 clinical studies are currently ongoing to investigate the PK of Cediranib when co-administered with a potent inhibitor (ketoconazole,

study D8480C00020) and a potent inducer (rifampicin, study D8480C00029).

On the basis of these data, the use of CYP inhibitors concomitantly with Cediranib is allowed.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF.

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

7.7.3 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF. Study treatment should be discontinued for a minimum of 3 days before the patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

7.7.4 Surgery

Since anti-angiogenetic drugs have been shown to interfere with reparation processes, any kind of surgical approach before or during the treatment must be scheduled according to the following guidelines:

- For elective surgery during the study, or any procedure that carries a risk of internal bleeding, it is recommended that Cediranib be stopped for 2 consecutive weeks prior to the surgical procedure. Cediranib treatment can be restarted when the surgical wound has healed. If emergency surgery is performed, precautions should be taken to minimise the potential risk of bleeding and thrombosis associated with this class of agents, Cediranib should be stopped and close monitoring for bleeding, wound healing and thromboembolic complications should be initiated. Patients should not receive Cediranib within 2 weeks of major abdominal or thoracic surgery.

7.7.5 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning

study treatment. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF.

7.8 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRFs.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer Olaparib-Cediranib. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of Olaparib and Cediranib at the appropriate scheduled visit, when new bottles will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF. Patients must return all containers and any remaining IP tablets at the end of the study.

7.8.1 Accountability

The investigational products provided for this study will be used only as directed in the study protocol.

The study personnel will account for all investigational products dispensed to and returned from the patient.

Study site personnel or the study monitor will account for everything received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction or return should be signed.

7.9 Discontinuation of investigational product

Patients may be discontinued from investigational products in the following situations:

- Patient's decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute

myeloid leukaemia (AML)

- Objective progression according to RECIST 1.1 criteria (unless in the investigator's opinion the patient is benefiting from the treatment and does not meet any other discontinuation criteria) or clinical progression
- If there is considered to be an unacceptable risk to subjects as judged by the investigator and/or the study Sponsor
- Subject lost to follow-up

7.9.1 Procedures for discontinuation of a subject from investigational product

By discontinuing from investigational products, the patient is not withdrawn from the study. If a patient is withdrawn from study, see Section 6.12.

At any time, patients are free to discontinue investigational product or withdraw from the study, without prejudice to further treatment.

A patient that decides to discontinue investigational products will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s).

Any patient discontinuing should be seen at 30 days post last dose for the evaluations outlined in the study schedule.

After discontinuation of investigational products, the Principal Investigator/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient.

Patients who discontinue treatment prior to documented RECIST progression should continue to be followed for progression as per the protocol schedule. Once progressed, all patients should be followed for PFS2 and OS as per the protocol schedule.

In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue study treatment, the study monitor must be informed immediately.

Patients will be required to attend the treatment discontinuation visit.

The patient should return all investigational products.

After discontinuation of the study treatment at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up. All new AEs and SAEs occurring during the 30 calendar days after the last dose of study treatment must be reported and followed to resolution as above. Patients should be seen at least 30 days after discontinuing the last dose to collect and / or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study medication should also be reported as an AE.

8. SAFETY REPORTING

The collection, assessment and presentation of safety reports will be carried out in accordance with the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3').

Patients will be carefully monitored for any AE occurring during the trial conduct. Such monitoring also includes clinical laboratory tests. AEs will be assessed in terms of their seriousness, severity, and causal relation to the study treatment. Safety reporting to study investigators, ECs, competent authorities will then follow in accordance with the results of such assessment.

8.1 Definitions

8.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with the study treatment. Any clinical manifestation of progression of the disease under study (including signs, symptoms or abnormal laboratory values) is not recorded as an AE. Likewise, a failure of expected pharmacological action is not considered an AE.

With the exception of the above, an AE can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease observed during the course of a clinical trial and the use of a medicinal product, whether or not considered related to the study drug;

- Any new disease or exacerbation of an existing disease that is different from the disease under study. Therefore a worsening in the character, frequency, or severity of a known condition should be classified as an AE;

- Recurrence of an intermittent medical condition (e.g., migraine) not present at baseline;

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug;

- Any symptom or medical complication related to a protocol-mandated intervention, including screening invasive procedures such as biopsies, placement of catheters and administration of contrast media.

Surgical procedures are not AEs because they are therapeutic measures. The condition for which the surgery is required is an AE, if it is different from the disease under investigation and occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition leading to these measures are not AEs, if the condition was known before the start of study treatment. In the latter case, the condition should be reported as medical history.

8.1.2 Adverse drug reaction

An ADR is defined as any untoward and unintended response to an investigational medicinal product (paclitaxel, Cediranib or Olaparib) related to any dose administered.

8.1.3 Serious adverse event or serious adverse reaction

The ICH guidance, "Clinical Safety Data Management: definitions and Standards for Expedited Reporting" (ICH E2A), defines a SAE as any untoward medical occurrence that at any dose:

- Results in death;

- Is life-threatening - an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe;

- Requires inpatient hospitalization - any patient admission to a health care facility, even if for less than 24 hours. Hospitalizations also include transfer within the

hospital to a different inpatient unit that are due to the occurrence of an AE. A planned hospitalization required by the protocol or programmed prior to study initiation does not constitute a SAE;

- Prolongation of existing hospitalization - Any extension of hospitalization beyond the anticipated;

- Results in persistent or significant disability/incapacity;

- Is a congenital anomaly/birth defect. A pregnancy during the study meets the seriousness criteria in the following cases: miscarriage, congenital anomaly, neonatal death, infant death.

- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above; examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse;

The terms "severe" and "serious" are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). On the other hand, the term "serious", describes patient/event outcome or action criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. For example, a headache that significantly interferes with the participant's usual functions might be assessed as "severe" in the clinical study documentation, but would NOT require reporting unless it meets one of the criteria for a SAE. Alternatively, a heart attack requiring admission to hospital may be assessed as mild, but would still be classified as serious because it meets the criteria for a SAE.

Severity and seriousness will be independently assessed for each AE and recorded on the e-CRF.

8.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR as a serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

- in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product

in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

Standard definitions for safety events are summarized in Table 9.

Table 9 Standard definitions of safety events

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: - results in death - is life-threatening - requires inpatient hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability/incapacity - consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: - in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product - in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

8.2 Adverse events

8.2.1 Adverse event management

In the present study, signs and symptoms of disease progression (including fatal outcomes) should not be reported as an AE.

The occurrence of AEs should be sought at each visit from the moment of performance of the first trial related procedure, including screening examinations and, subsequently at each study visit. AEs may be spontaneously reported by the patient during the screening process or during study visits, investigated through non-directive questioning of the patient regarding periods between visits, or directly observed through physical examination, laboratory tests, or any other relevant assessment.

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded in the patient file and on the eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent: assessment of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it and the outcome should be made at each visit (or more frequently, if necessary).

8.2.2 Adverse event notification

AEs notification will be carried out completing the relevant page on the study eCRF. It is recommended that notification is done once the information regarding each AE is complete. Any time new information becomes available or when one or more of the AE characteristics is modified (i.e. severity, seriousness and/or outcome), such new information should be entered onto the same AE record.

Vice versa, the repetition of the same AE after its resolution should be reported as two separate events. For example, liver enzyme alterations that are present in two consecutive visits will be reported as a single AE, and the worst severity recorded. On the contrary, a second transaminase elevation that appears after normalization of the blood picture will be reported as a second hepatic event.

8.2.3 Adverse event assessment and reporting

All AEs will be recorded by the investigator. Detailed information on all AEs will be recorded in the patient's clinical chart and the required information entered onto the relevant page of the eCRF.

In particular, all information concerning the following AE characteristics should be minutely and timely registered and updated as necessary:

- Diagnosis
- Seriousness
- Severity
- Causal relation to study treatments
- Start date
- AE management information
- Outcome

In addition, the following variables will be collected for SAEs as applicable:

- Date AE
- Met criteria for serious AE
- Date Investigator became aware of serious AE
- Seriousness criteria
- Narrative Description
- Causality assessment in relation to Study procedure(s)
- For fatal SAEs:

a. Date of death
b. Probable cause of death
c. Autopsy performed

8.2.4 Diagnosis

Whenever possible, AEs (including laboratory abnormalities that constitute AE) should be described using a diagnosis, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

All AEs should be classified according to the << NCI CTCAE (version 4) criteria>>. Classification should include the <<NCI-CTC AE>> official clinical or laboratory categories, followed by the specific clinical parameters as listed in the relevant severity grading table.

8.2.5 Seriousness

The seriousness criterion will be applied to any AE that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect or is an important medical event ad defined above.

The initial seriousness and severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

Any AE which fulfils one or more of the seriousness criteria listed above, should be treated as SAE and the clinician observing the event should complete the SAE form and follow the expedited SAE notification procedures indicated below.

8.2.6 Severity

Severity of AEs will be assessed according to the NCI-CTC AE grading reported in Table 10.

AEs separate from the progression of disease (example, deep vein thrombosis at the time of progression) will be reported as per usual guidelines used for such events with proper attribution to the study drug.

Only in the case where NCI-CTC AE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening, and fatal corresponding to grades 1-5, will be used, and classified as follows:

Table 10 NCI-CTC AE grading

Grade 1: Mild	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2: Moderate	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3: Severe	Symptoms causing inability to perform usual social & functional activities
Grade 4: Potentially Life-threatening	Symptoms causing inability to perform basic self-care functions or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5: Fatal	

8.2.7 Relationship to study agents

The site investigator is responsible for assessing the relationship between the AE and the study agents. Site investigators must determine whether there is a reasonable possibility that the study agents caused or contributed to an AE/SAE.

The relationship assessment should be based on clinical judgment and should involve evaluation of the following criteria:

- The temporal relationship between the event and administration of the study treatment;
- A plausible biological mechanism for the agent to cause the AE;
- All other possible etiologies for the AE;
- Previous reports of similar AEs associated with the study treatment or other agents in the same class;
- Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable;

Investigators shall use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, using the standard available attribution categories.
The investigator should express his/her level of confidence in the assessment of the causal relationship of an event to study treatment using the terms reported in Table 11.

Since the study treatment is administered as part of a drug combination (for the experimental arms), the attribution assessment will be made for each component of the combination.

Table 11 Assessment of causality

Attribution categories	Description
Certain	AE has a plausible time relationship to study drug(s) intake; the event cannot be explained by disease or other concomitant drugs; Response to drug(s) withdrawal plausible, rechallenge satisfactory (if necessary)
Probable	AE has a reasonable time relationship to study drug(s) intake; the event can be unlikely attributed to disease or other concomitant drugs; Response to drug(d) withdrawal clinically reasonable, rechallenge not required
Possible	AE has reasonable time relationship to study drug intake; the event could also be explained by disease or other concomitant drugs; information on drug withdrawal may be lacking or unclear
Unlikely	AE with a time to drug intake that makes a relationship improbable (but not impossible); other plausible explanations exist
Unrelated	AE with a time to drug intake that makes a relationship impossible; other plausible explanations exist
Conditional/Unclassified	Event or laboratory test abnormality; more data for proper assessment needed or additional data under examination
Unassessable / Unclassifiable	Report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory; data cannot be supplemented or verified

8.2.8 Expectedness

Expectedness will be classified by the Sponsor on the basis of the reference documents of study drugs.

8.3 Reporting

8.3.1 SAE

To ensure patient safety, every SAE, regardless of suspected causality, occurring from the signature of the informed consent until the date of last visit must be reported to sponsor within 24 hours of learning of its occurrence.

All identified SAEs must be recorded and described on the appropriate SAE form of the eCRF. The investigator will notify the sponsor safety desk all SAEs occurring during the treatment period. All forms must be dated and signed by the responsible investigator or sub-investigators and sent by email or fax within 24 hours of the initial observation of the event to the Sponsor safety desk:

Laboratory of Methodology for Clinical Research

IRCCS-Istituto di Ricerche Farmacologiche Mario Negri

Study Safety Desk

email: safetydesk.rc@marionegri.it

Fax: + 39 02 33200231

Any new or additional information regarding the SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. Once a SAE is detected, it should be followed until its resolution or until it is judged to be permanent. Follow-up information is sent to the same contact(s) to whom the original SAE report form was sent, using a new SAE report form stating that this is a follow-up to the previously reported SAE.

The repetition of the same SAE after its resolution should be reported as two separate events.

8.3.2 Olaparib adverse events of special interest

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of Olaparib safety profile and require close monitoring and rapid communication by the investigators to the Sponsor. An AESI may be serious or non-serious. AESI for Olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to Sponsor safety desk whether it is considered a non-serious AE [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

A questionnaire will be sent to any investigator reporting an AESI, in order to provide further detailed information about the event. It is possible that other events, arising during the study, should be identified as AESIs; these events will require the use of the questionnaire with the aim to evaluate the event and its relation to Olaparib.

8.3.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The management of suspected unexpected serious adverse reactions (SUSARs) will be done according to the guideline 2011/C 172/01 "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')" based on Article 18 of directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

According to the CT-3, the SUSARs will be notified via EudraVigilance to Competent Authorities (EMA and AIFA) and to the Marketing Authorization Holder (MAH):

- within 7 days if the SUSAR results in death or is life-threatening
- within 15 days if the SUSAR is not fatal and not life-threatening

For this purpose, the Mario Negri Institute is registered to EudraVigilance as Sponsor of not-for-profit clinical trials.

All SUSARs will be notified to the Coordinating Ethics Committee and to the trial Investigators.

8.4 Deaths

In this study, deaths due to disease progression will not be classified as SAE. With this exception, all on-study deaths, regardless of relationship to study drugs, must be recorded on the SAE form and immediately reported to the Sponsor. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE form. Generally, only one such event should be reported. The term "sudden death" should

only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death later becomes available (e.g. after autopsy), "sudden death" should be replaced by the established cause of death.

8.5 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

There is currently no specific treatment in the event of overdose with Olaparib-Cediranib combination and possible symptoms of overdose are not established.

Both drugs must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 200 mg BD of Olaparib and 30 mg/day of Cediranib.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE form. If the associated AE fulfills seriousness criteria, the event should be reported using SAE form to the Sponsor within 24 h from learning of the event.

8.6 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of first informed consent, throughout the treatment period and including the follow-up period (30 days after the last dose of study drugs). During the course of the study all AEs and SAEs should be proactively followed up for each participant. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

The investigator is responsible for following all SAEs until resolution, until the participant returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

For Pharmacovigilance purposes and characterisation of AESI, ANY case of MDS/AML, new primary malignancy occurring after the follow up period should be reported to Sponsor safety desk whether it is considered a non-serious AE [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.
At any time after a patient has completed the study, if an investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify the event to Sponsor safety desk.

8.6.1 Follow-up of unresolved adverse events

Any AEs that are unresolved at the participant's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

8.7 Reporting requirements for pregnancies

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the study drug at any time during pregnancy, is suspected. Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) occurring while the patient is on study drug, or within 30 days of the patient's discontinuation visit, are considered reportable events.

8.7.1 Maternal exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor safety desk immediately and always within 24 hours from first knowledge.

Immediately after detecting a case of suspected pregnancy in a clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

The Investigator will follow the pregnancy until its outcome, and must notify the Sponsor safety desk the outcome of the pregnancy as a follow-up to the initial report. For any event during the pregnancy, which meets a seriousness criterion, the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the study safety desk

within 24 hours of the Investigator's knowledge of the event). All spontaneous miscarriages, congenital abnormalities or birth defects and neonatal deaths that occur within 30 days from birth without regard to causality and any infant death that the Investigator suspects to be related to exposure to the study drug should be reported, as SAE, within 24 hours from the Investigators' knowledge of the event. The outcome of all pregnancies should be followed up and documented even if the patient was discontinued from the study.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Participant data protection.

9.2 Compliance with Laws and Regulations

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the International Conference on Harmonization consolidated Guideline E6 for Good Clinical Practice and applicable regulatory requirement(s) including the following:

- Ministerial Decree 15-07-1997 (Recepimento delle linee guida dell'Unione europea di buona pratica clinica per l'esecuzione delle sperimentazioni cliniche dei medicinali);
- Regulation (EU) N. 536/2014 Of The European Parliament And Of The Council Of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC;
- Legislative Decree 08-11- 2012, n. 189 (Conversione in legge, con modificazioni, del decreto-legge 13 settembre 2012, n. 158, recante disposizioni urgenti per promuovere lo sviluppo del Paese mediante un più alto livello di tutela della salute);
- Decision AIFA 20-09-2012 (Adozione delle linee guida CT-3 (giugno 2011) della C.E. di attuazione della Direttiva 2001/20/CE, delle linee guida ICH E2F (settembre 2011) e istituzione di una banca dati nazionale relativa al monitoraggio della sicurezza dei medicinali in sperimentazione clinica. (Determinazione n.9/2012);
- Decision AIFA 07-03-2011 (Modifica delle appendici 5 e 6 al decreto del Ministro della salute 21 Dicembre 2007 concernente i modelli e le documentazioni necessarie per inoltrare la richiesta di autorizzazione, all'Autorità Competente, per la comunicazione di

emendamenti sostanziali e la dichiarazione di conclusione della sperimentazione clinica e per la richiesta di parere al Comitato Etico);

- Ministerial Decree 07-11-2008 (Modifiche ed integrazioni ai decreti 19 Marzo 1998, recante «Riconoscimento della idoneità dei centri per la sperimentazione clinica dei medicinali»; 8 Maggio 2003, recante «Uso terapeutico di medicinale sottoposto a sperimentazione clinica» e 12 Maggio 2006, recante «Requisiti minimi per l'istituzione, l'organizzazione e il funzionamento dei Comitati Etici per le sperimentazioni cliniche dei medicinali»);

- Legislative Decree 06-11-2007, n. 200 (Attuazione della direttiva 2005/28/CE recante principi e linee guida dettagliate per la buona pratica clinica relativa ai medicinali in fase di sperimentazione a uso umano, nonché requisiti per l'autorizzazione alla fabbricazione o importazione di tali medicinali);

- Ministerial Decree 17-12-2004 (Prescrizioni e condizioni di carattere generale, relative all'esecuzione delle sperimentazioni cliniche dei medicinali, con particolare riferimento a quelle ai fini del miglioramento della pratica clinica, quale parte della assistenza sanitaria);

- Legislative Decree 24-06-2003, n. 211 (Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico);

- Ministerial Decree 08-02-2013 (Criteri per la composizione e il funzionamento dei comitati etici);

- Ministerial Decree 12-05-2006 (Requisiti minimi per l'istituzione, l'organizzazione e il funzionamento dei Comitati Etici per le sperimentazioni cliniche dei medicinali);

- Ministerial Decree 21-12-2007 (Modalità di inoltro della richiesta di autorizzazione all'Autorità competente, per la comunicazione di emendamenti sostanziali e la dichiarazione di conclusione della sperimentazione clinica e per la richiesta di parere al comitato etico);

- Authorization n. 9/2014 (Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica);

- Decision 24-07-2008, n. 52 (Linee guide per i trattamenti di dati personali nell'ambito delle sperimentazioni cliniche di medicinali);

- Legislative Decree 30-06-2003, n. 196 (Codice in materia di protezione dei dati personali);

- Ministerial Decree 14-07-2009 (Requisiti minimi per le polizze assicurative a tutela dei soggetti partecipanti alle sperimentazioni cliniche dei medicinali).

9.3 Ethics and regulatory review

The coordinating Independent Ethics Committee (IEC) should approve the final study protocol and related study documents including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The final study protocol and the associated study documentation including the final version of the Informed Consent Form, should be approved by the National regulatory authority, according to local regulations.

9.4 Informed consent

At screening, the Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that she is free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.

At baseline, the Principal Investigator(s) at each centre will:

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File and are available for verification by study monitors at any time
- Ensure a copy of the signed Informed Consent Form is given to the patient

The informed consent process should be documented in the medical record. The date that informed consent was given must be recorded on the eCRF.

9.5 Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number.

This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IEC for each study site, as appropriate.

9.6 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and the national regulatory authority before implementation.

9.7 Audits and inspections

Authorised representatives of a regulatory authority or Ethics Committee may perform audits or inspections at the study centres, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements.

9.8 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs, ICFs, Investigator Site Files (ISFs) must be retained by the Principal Investigator for at least 7 years after completion or discontinuation of the study, or for the length of time required by relevant

national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, participant to local regulations.

No records may be disposed without the written approval of the Sponsor.

Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

10. DATA MANAGEMENT

10.1 Source Data

Source documents are where data is first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions.

On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code.

10.2 Access to on trial patient Data and Study eCRFs

Direct access to source data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Access to the study clinical data entry platform will be granted to trial staff through a computer-based credential generation system in the following manner:

- Study centre staff: will be granted access to own centre data entry manual for all participants. Centre credentials will be assigned to staff recorded in the PI signed "Centre Delegation Form" as responsible for data entry. Centre staff credentials also allow for participant registration and randomization. Centre credentials will become active following specific centre staff training operated by the coordinating CTU staff, and attested in a specific training log. Each centre can receive up to three credentials for data entry.

- Centre PIs: will be granted Centre data entry credentials to allow for electronic signature of SAE forms, completed CRFs and meta-data entries which require PI approval (i.e. protocol deviations).

- Study administrators: study administrator / data managers operate at the study coordinating CTU (IRFMN). Study administrators will be granted credentials allowing for viewing AND modification of data on all study participants. Study administrators credentials do not allow participant registration / randomization. Study administrators credentials shall not be used for data entry unless specific opportunities require central interventions, and centre PI provides written authorization for data entry/modification at IRFMN.

- Study Auditors: study auditors include all coordinating CTU staff with the exception of study administrators. Study auditors can be study coordinators, reviewers, quality assurance staff, study statisticians. Auditor credentials allow for viewing of data for all study participants. Auditors credentials do not allow for CRF modifications

- Study monitors: Auditor credentials allow for viewing of data for all study participants. Monitors credentials do not allow for CRF modifications with the exception of the "monitoring check" button.

- Centralized staff: staff credentials allow for viewing and modification of specific study CRFs created for entering information on centralized study procedures.

10.3 Data Recording

Data collection will be performed using electronic CRFs exclusively. No paper CRFs are provided to study investigators.

10.4 eCRFs and Clinical Data Management Application (CDMA)

The eCRF will be handled by HeavyBase (url: http://www.heavybase.org), an open source push based "peer to peer" data management system.

HeavyBase is an integrated database for managing clinical data that is in full compliance with Food and Drug Administration regulations 21 CFR part 11. In particular, Heavybase is capable of complete tracking and documentation of data entries and modification. Heavybase allows users to enter data both online, as with a web-based system, or off-line in case of temporary lack of internet connectivity.

This is feasible because HeavyBase stores in the local CDMA a the complete set of data, which is then transmitted to the central study coordination any time the computer is connected to the network.

The system requires no installation and does not require administrator access rights to the computer. It can be downloaded from: http://lsi.marionegri.it/trials/nomestudio/. The single executable file (nomestudio.exe) can be saved on the desktop, and used directly without any configuration.

Data security is guaranteed by redundancy. When the database is activated on a computer linked to the network an encrypted copy of the data is replicated in all other active installations. Data safety is then ensured by strong encryption (256 bit AES with hashed 256 bit key) of all data rendering all data that is not permitted by the centre credentials, unreadable to the user.

10.5 Site training and Data Entry support tools

All eCRFs should be completed by designated, trained site staff. Upon completion of the study delegation form, site CDMA users will receive training by phone call from study coordination LSI staff. Following completion of training, user credentials will be activated.

The following forms of user assistance shall be available to assist site staff in operating the CDMA and entering data:

- Hard copy Heavybase user manual detailing the system features, installation and correct handling
- Hard copy eCRF completion manual, with detailed instruction for CRF use
- CDMA loaded description of each single field present in the eCRF. Field description and instructions will become visible whenever users place the cursor on the field they wish to complete.
- Appointed Sponsor Trial manager
- LSI help desk, available by phone during office hours at: 02-3901 4514

10.6 Data quality assurance

Study sites shall enter trial data onto the eCRF in a truthful, accurate and timely manner. All entered data shall be abstracted from source documents that will be kept in the study

participant's clinical chart and be made available to Sponsor appointed monitors in case of verification.

Data entry timing shall follow closely the protocol's timeline for activities and procedures. As a rule, time lapse between activity and data entry should not exceed 7 working days for clinical procedures or 15 working days for diagnostics and laboratory examinations to allow site staff to retrieve results. All efforts should be made to avoid creation and accumulation of data back log.

Correct data transmission is essential to trial management, data quality and site monitoring operations. To ensure fluent transmission of entered data to and from the site, as well as timely updates to the study CDMA, sites shall maintain the study CDMA active during all working hours of all working days throughout the study.

Data quality assurance consists of three levels of intervention:

- Data entry (front end) edit checks and queries. Front end checks include prompts for missing data, quality warnings comparing data to protocol requirements, checks for correct timing of procedures, range checks data values and cross checks for incongruent data. These real time data quality checks will become visible each time the user saves the data. Therefore it is highly advisable that users press the save button upon completion of each eCRF page and check entered data for quality before moving onto the following eCRF section

- Data quality queries (back end). These checks will be periodically sent to site staff by the trial manager by means of Data Clarification Forms (DCF). All efforts shall be made to ensure prompt and exhaustive resolution of all queries

- On site monitoring (described in Section 11)

10.7 Record Keeping

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

11. MONITORING OF THE STUDY

11.1 Source data

During the study a Sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples have been collected and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The Sponsor representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained according to the policy for retention of records described in Section 9.8.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and competent authorities and IEC review. The investigational site must also allow inspection by applicable health authorities.

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

The monitor is responsible for visiting sites at regular intervals (as detailed in the Trial Monitoring Plan) throughout the study to verify adherence to the protocol: completeness, accuracy, and consistency of the data, and adherence to ICH/GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to participant medical records and other study-related records needed to verify the entries on the eCRFs.

The principal investigator and all the staff will be available to answer to any issue arising during the monitoring visits (e.g. radiologist for the disease assessment evaluation, pharmacist for the drug accountability).

The monitor will communicate deviations from the protocol, SOPs, ICH/GCP and applicable regulations to the investigators and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are documented and addressed.

11.2 Study Initiation Visit

In each center, after the completion of the CDMA training by the LSI staff, a Site Initiation Visit (SIV) will be performed by phone by an appointed Sponsor monitor. All personnel recorded in the study delegation form (e.g. Principal Investigator, Co-Investigators, radiologist, pharmacist, clinical research coordinator, research nurses) shall attend the SIV.

12. STUDY MANAGEMENT

12.1 Administrative Structure

This study is sponsored by the IRCCS Istituto di Ricerche Farmacologiche Mario Negri.Ten experimental centers will participate in this study. The Sponsor will provide clinical operations oversight, data management support, and clinical monitoring.

The study Sponsor will allocate qualified personnel to the present trial. All the figures involved in the study design, management and conduct are qualified according to Italian laws and regulations concerning clinical trials, and specifically trained on the objectives, procedures and instruments of this trial.

The Principal Investigator is responsible for the management of this study at each site.

12.2 Training of study site personnel

The Principal Investigator of each sites will ensure that appropriate training relevant to the study is given to all investigational staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

12.3 Independent Data Monitoring Committee (IDMC)

An independent IDMC composed of three international experts (two oncologists and one statistician), not involved in the study and with no conflict of interest with respect of study results will monitor the progress of the study on ethical and scientific basis.

Specific tasks of IDMC will be:

- To review study progress (i.e. accrual rate, protocol compliance, event rate);
- To monitor toxicity. The IDMC will review interim toxicity data although this is primarily the responsibility of the SC. To examine other trials. The IDMC will review reports of related studies performed by other groups or organizations to determine whether such information affects the aims or preliminary findings of the trial;
- To review any major modification to the study proposed by the SC prior to its implementation.

12.4 Publication of Data

Results derived from the trial are property of the Sponsor which shares them with all participating investigators.

Every publication of the trial results will be written on the basis of the analyses performed by the Sponsor. Publications will be decided by the Sponsor. Authors to be reported in the front page will be selected on the basis of the specific contribution or the number of enrolled patients, on the consistency, completeness and accuracy of the data. The name list at the end of each article will include all the other participants who contributed to patients enrollment or to study coordination, monitoring and data analysis. Furthermore, all manuscripts will include an appropriate acknowledgment section.

Rules for abstract presentation will be the same as for extended papers.

12.5 Clinical Study Report

At the end of the study, clinical study report will be written and distributed to all investigators.

12.6 Finances

The study is Sponsored by the IRCCS Istituto di Ricerche Farmacologiche "Mario Negri" which plays the role of not-for-profit sponsor.

AstraZeneca supports the study, providing the economical support for costs related to insurance, clinical sites activation, study coordination, remote data capture system development and maintenance, data management, local and central monitoring, statistical analysis and reporting of study results.

No funds will be provided to IECs in accordance to the DM 17-12-2004.

12.7 Insurance

The Sponsor of the study agrees to take out adequate clinical insurance to cover its obligations, including but not limited to provide compensation to patients in the study suffering injury of death or loss caused by the administration of drugs or any clinical intervention or procedure in accordance with the relevant protocol and all legal requirements. All patients participating in this clinical trial will therefore be covered by a civil liability policy in accordance to the DM 14-07-2009.

12.8 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study.

The study is expected to start in Q1 2017 and to end by Q3 2019.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. The study may also terminate prematurely if concerns for safety arise within this study or in any other study with study drugs. When the final analysis can be performed, the clinical study database will closed to new data. Patients who are receiving treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit, patients may continue to receive investigational product. All patients will receive follow-up care in accordance with standard local clinical practice. For patients who do continue to receive treatment beyond the time of the final data cut-off, investigators will continue to report all SAEs to Sponsor Safety desk until 30 days after study treatment is discontinued, in accordance with Section 8.3.1(Reporting of Serious Adverse Events).

Additionally as stated in Section 8.6.1, any SAE or non-serious AE that is ongoing at the time of this data cut-off must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

13.1 Description of analysis sets

13.1.1 All Patients Analysis Set

The All Participants Analysis Set is defined as all participants who provided informed consent and were enrolled in the study. The listings of all variables will be based on the All Participants Analysis Set.

13.1.2 Intent-to-Treat (ITT) Analysis Set

The ITT analysis set is defined as all randomized patients, without major violations of eligibility criteria. Patients will be analyzed according to randomization arm.

Major violations in the eligibility criteria will be evaluated on a case by case basis in a pre-analysis meeting in order to define the population.

13.1.3 Per-Protocol (PP) Analysis Set

The PP analysis set is defined as all patients of the ITT analysis set, who received at least 4 weeks of treatment, unless they interrupted before for disease progression or death. Patients randomized to the control arm, receiving the experimental treatment and patients randomized to the experimental arm, receiving the control treatment will be excluded.

13.1.4 Safety Analysis Set

The Safety Analysis Set is defined as all patients included of the ITT Analysis Set, who received at least one dose of study treatment, whether withdrawn prematurely or not. Patients will be considered in the treatment arm they actually received.

13.2 Methods of statistical analyses

13.2.1 Efficacy Analyses

Primary endpoint analysis will be performed on ITT analysis set.

As secondary analysis, PFS will be analysed also on PP analysis set.

The analysis of ORR will be performed on patients included in the ITT analysis set, receiving at least one dose of study treatment and with at least one radiological assessment. Radiological assessment will be evaluated in accordance to RECIST criteria.

PFS2 and OS will be performed on ITT and PP analysis set.

PFS, PFS2, OS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS, PFS2 and OS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

ORR will be described providing the absolute and relative frequencies of patients with CR or PR, according to RECIST criteria; the 95% CI will be computed by means of exact binomial methods.

Quality of life will be evaluated by FACT-O questionnaire. Change scores in quality of life (i.e. differences from baseline to each visit) will be calculated and described at every visit and at the time of study discontinuation, for each domain and within each arm.

A mixed model will be used to assess differences in quality of life scores among groups and the interaction between time and treatment.

When the target number of events for PFS will be reached (Section 13.3), the following conclusions will be possibly drawn:

- if both arms demonstrate the superiority over control arm in terms of PFS, the best schedule will be selected based on safety profile considering in particular the mean number of evacuations per day.
- if only one experimental arm demonstrate the superiority over control arm in terms of PFS, there will be the positive effect only for that treatment schedule.
- if both arms do not demonstrate the superiority over control arm in terms of PFS, there will be less than desired effect for both experimental arms and the combination of Cediranib and Olaparib will not be considered for further studies in this set of patients.

13.2.2 Safety Analyses

The primary safety analysis will be conducted on the safety analysis set excluding patients who interrupted the treatment before 4 weeks, unless the interruption is due to diarrhea.

In case both arms will demonstrate the superiority over control arm in terms of PFS, the best schedule will be selected based on safety profile considering in particular the mean number of evacuations per day. The difference on mean number of evacuations per day will be tested through a t-test test for two independent groups. If the normality assumptions cannot be assumed a non parametrical test will be performed.

The assessment of safety will be mainly based on adverse reactions (ARs) and the frequency and nature of SAEs and will be conducted on the safety analysis set.

For each patient and for each type of adverse event, the worst degree ever suffered during treatment will be used for the analysis.

All safety parameters (including diarrhea) will be presented and analyzed in terms of listings and summary tables.

SAEs will be summarized by presenting the number and percentage of patients having any SAE and having an SAE in each system organ class. Other information collected (e.g. severity or suspected relationship to study medication) will be listed as appropriate.

13.2.1 Compliance Analyses

The compliance to treatment and the dose intensity will be evaluated as number of cycles given, the modification of dose and reasons for ending the treatment will be tabulated and described on ITT analysis set.

13.2.2 Interim analyses

There are no formal interim analyses planned for this study.

Any safety issue that could affect study conduct will be communicated in a timely manner to the investigators and to Institutional Review Boards (IRBs)/Ethics Committees (ECs).

13.3 Determination of sample size

Assuming a median PFS in the control arm of 3.4 months (AURELIA trial control group) [20], this study is designed to detect an HR of 0.51 that corresponds to an advantage in PFS of 3.3 months. With one-sided 5% significance level and with at least 80% power, approximately 60 patients (55 events) for each comparison are estimated to be enrolled. Considering the two pre-planned comparisons (intermittent vs paclitaxel and continuous vs paclitaxel) a total of 90 eligible patients are needed.A better toxicity profile (especially intestinal tolerability) for the intermittent schedule than the continuous schedule is plausible but lacks empirical evidence. A mean reduction of two evacuations a day over the first four weeks of treatment can be considered as clinically relevant. Considering the number of patients required for the PFS comparison, and a 5% of patients not evaluable for the primary safety endpoint, an effect size equal to 1 (assuming a standard deviation equal to 2) could be detected with a power greater than 90% and a one sided first-type error (alpha) equal to 5%. Since the comparison in safety will be performed only if both experimental arms will demonstrate the superiority in terms of PFS over the control arm, an alpha adjustment is not required.

Taking into account a 10% of patients not evaluable for the primary efficacy endpoint, it will be necessary to enrolled approximately 100 patients.

13.4 Data monitoring committee

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts and a statistician and do not have any major conflict of interest. Following the review the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a

recommendation, a report will be provided to Coordinator Study Board. The report will only include the recommendation and any potential protocol amendments.

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Appendix 1 - Study Schedule

Visit Number	Screening visits 1		2	3	4	5	6	Visit n°7/ onwards Subsequent treatment visits every 4 weeks[a]	Discontinuation of study treatment	Safety Follow-up 30 days after last dose of IP	Follow-up If treatment discontinued due to reasons other than disease progression	2nd progression (PFS2) and Survival follow-up
Day	**Part 1**	**Part 2**	**1**	**8**	**15**	**22**	**29**	**Day 1 of next visit period (visit 7 equals day 57–week 8; visit 8 equals day 85-week 12; etc)**	**30 days after the last dose of study treatment**			
Visit Window	*-28 to -1 days*	*-7 to -1 days*		*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*±7d*	*±7d*	*±7*	*±7*
Informed consent	x											
Blood sample for determination of BRCA status [b]		x										
Inclusion/exclusion criteria	x	x										
Medical and surgical history	x	x										
Prior cancer therapies including radiotherapy	x											
ECOG performance status	x		x				x	x	x		x	x
Physical exam[c]		x	x				x	x	x			
Vital signs (including **blood pressure**, pulse and temperature) [d], **body weight and ECG**[e]		x	As clinically indicated									
Haematology/clinical chemistry[f]		x	x	x	x	x	x	x	x	x		
Urinalysis		x	x				x	x				
Pregnancy test	x		x									
Tumour Assessment (CT or MRI according to RECIST v1.1) [g]	x							Every 8 weeks for 48 weeks and every 12 weeks thereafter until PD.	x	x	Every 8 weeks for 48 weeks and every 12 weeks thereafter until PD.	
Blood sample for disease specific marker (CA-125)	x		x				x	x	x		x	
Adverse Events[h]	x[i]										x	x
Concomitants medications	x		x	x	x	x	x	x	x	x		
FACT-O[j]			x				x	x	x			
Subsequent therapies/ Time to second progression/ Survival									x	x	x	x

a. Visit to take place on Day 1 of a 4 weeks (28 days) visit period up to 52 weeks (if not progressed and still on treatment), then on day 1 of a 12 week visit period relative to date of randomization. Visits for patients who remain on treatment post progression should take place every 12 weeks.

b. Only for patients not previously tested

c. Physical examination should be performed according to the schedule, after the baseline assessment it is not necessary to record the details on an eCRF. Any clinically significant changes should be recorded as adverse events.

d. Vital signs at screening and then if clinically indicated during study treatment. Blood pressure (BP) should be monitored at each visit during the treatment and at the end-of treatment visit. Moreover the patient should record BP on the home-diary during the study treatment period.

e. ECG at screening and then if clinically indicated. ECG should be performed once the patient has been in the supine position at least 5 minutes in each case.

f. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but whithin 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly. Coagulation tests only required if clinically indicated. For a list of all required laboratory tests please refer to Section 6.5. Safety bloods will be taken at the 30-day FU visit as well. .

g. Follow-up assessments will be performed every 8 weeks (±1 week) up to 48 weeks, then every 12 weeks (±1 week) relative to date of randomization. Follow-up CT or MRI assessment will cover chest (in those patients with disease in the chest or upper abdomen lymphadenectomy at baseline), abdomen and pelvis. Any other sites at which new disease is suspected should be also be appropriately imaged. Patients must be followed until RECIST disease progression.

h. When an AE for nausea and vomiting occurs, an additional eCRF will require completion. All ongoing adverse evnts/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow-up period after last dose of study medication must be followed to resolution.

i. Only SAE's related to blood sampling for the *g*BRCA test will be collected at this visit

j. FACT-O will be collected at baseline and every 4 weeks for the first six months or until treatment discontinuation whichever comes first

Appendix 2 - FACT-O (Version 4)

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 past 7 days.**

	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

English (U.S.) version1
Copyright © 1987, 1997

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>.

	<u>EMOTIONAL WELL-BEING</u>	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

	<u>FUNCTIONAL WELL-BEING</u>	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

English (Universal)
Copyright 1987, 1997

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**
[illegible]	I have swelling in my stomach area	0	1	2	3	4
[illegible]	I am losing weight	0	1	2	3	4
[illegible]	I have control of my bowels	0	1	2	3	4
[illegible]	I have been vomiting	0	1	2	3	4
[illegible]	I am bothered by hair loss	0	1	2	3	4
[illegible]	I have a good appetite	0	1	2	3	4
[illegible]	I like the appearance of my body	0	1	2	3	4
[illegible]	I am able to get around by myself	0	1	2	3	4
[illegible]	I am able to feel like a woman	0	1	2	3	4
[illegible]	I have cramps in my stomach area	0	1	2	3	4
[illegible]	I am interested in sex	0	1	2	3	4
[illegible]	I have concerns about my ability to have children	0	1	2	3	4

Appendix 3 - RESPONSE EVALUATION CRITERIA IN SOLID TUMORS V.1.1

Response Criteria by RECIST v.1.1 (Eisenhauer 2009)

Evaluation of Target Lesions

- CompleteResponse(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 the diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 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 progressions).
- 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

Evaluation of Non-Target Lesions

- CompleteResponse(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)
- Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- ProgressiveDisease(PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
- Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

- 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 response assignment will depend on the achievement of both measurement and confirmation criteria.

RECIST CRITERIA in patients with Measurable Disease (ie, Target Disease)

Target lesions	Non-Target lesions	New lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Duration of Response

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 progressive disease is objectively documented.

Duration of SD: SD 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, including the baseline measurements.