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Canolfan Ymchwil Treialon

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor: University of Manchester			
Name	Position	Signature	Date
Dr Mohammed Zubair	Research Governance, Ethics and Integrity Manager	Approved by email	14/10/2021
Director: Prof Richard Adams			
Name	Signature		Date
Prof Richard Adams	Approved by email		12/10/2021
Chief Investigator: Prof Gordon Jayson			
Name	Signature		Date
Prof Gordon Jayson	Approved by email		25/10/2021

General Information This protocol describes the CEBOC clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to the trial team at the CTR via the main trial email address.

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Trial Co-ordination:

The CEBOC trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the CEBOC Trial Management Group (TMG). For **all queries** please contact the CEBOC team through the main trial email address. Any clinical queries will be directed through the Trial Manager (TM) to either the Chief Investigator or a Co-Investigators

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Registration:

Registration
To Register a participant email CEBOC@cardiff.ac.uk
from Monday – Friday between 0900 - 1700
(See section 9.5 for more details).

Clinical queries:

Clinical queries
CEBOC@cardiff.ac.uk
All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to CTR Safety Team within 24 hours of becoming aware of the event (See section 13 for more details).

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Glossary of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
APPT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AUC	Area Under Curve
AZ	AstraZeneca
BD	Bi Daily
BP	Blood Pressure
BRCA	Breast Cancer Gene
CA	Competent Authority
CI	Chief Investigator
Cmax	The maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administrated and before the administration of a second dose.
CrCl	Creatinine Clearance
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DBP	Diastolic Blood Pressure
DIC	Disseminated Intravascular Coagulation
DLT	Dose Limiting Toxicity

DM	Data Manager
DSB	Double Strand Breaks
DSUR	Development Safety Update Report
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group (Performance Status)
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration
GI	Gastrointestinal Illnesses
GMP	Good Manufacturing Practice
GP	General Practitioner
Hb	Haemoglobin
HGSOC	High Grade Serous Ovarian Cancer
HRA	Health Research Authority
HRCT	High Resolution Computed Tomography
HRR	Homologous Recombination Repair
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INR	International Normalized Ratio
IQR	Interquartile Range
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	The Intention-to-Treat
IV	Intravenous

LD	Longest Diameter
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MA	Marketing Authorisation
MAD	Maximum Administered Dose
MDS	Myelodysplastic Syndrome
MHRA	Medicine and Healthcare products Regulatory Agency
MI/CVA	Myocardial Infarction / Cerebral Vascular Accident
MRC	Medical Research Council
MS	Member State
MTD	Maximum Tolerated Dose
NHS R&D	National Health Service Research & Development
OD	Once Daily
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Physical Exam
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Participant Information Sheet
QL (QoL)	Quality of Life
QP	Qualified Person for release of trial drug
REC	Research Ethics Committee
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RP2D	Recommended Phase II Dose
RPLE	Reversible Posterior Leuko-Enchephalopathy
RSI	Reference Safety Information
RTKi	Receptor Tyrosine Kinase Inhibitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure

SDV	Source Document Verification
SGOT	Serum Glutamic Oxaloacetic Transaminase
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFST	Time to first subsequent chemotherapy
TFTs	Thyroid Function Test
TKI	Tyrosine Kinase Inhibitor
TM	Trial Manager
tmax	Time to second subsequent chemotherapy
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSST	Time to second subsequent chemotherapy
UGT	Uridine di-phosphoglucuronosyl
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	VEGF Receptor
WOCP	Women of Childbearing Potential

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
Not applicable	1.0	06/10/2017	Not applicable, first version of protocol
Not applicable	2.0	16/11/2017	V1.0 MHRA required more justification for olaparib dose
	3.0	02/03/2020	Amended inclusion criteria from 'measurable disease' to 'evaluable disease'
	3.0	02/03/2020	• Added exclusion criteria for patients previously treated with weekly paclitaxel for platinum resistant disease. • Addition of exclusion criteria; exclude cytotoxic therapy within 4 weeks of olaparib. • Removal of D8 and D15 visit post paclitaxel nab-paclitaxel • Alteration to timing of CT scan. • Adequate haematological function: Hb ≥ 90 g/l, Neutrophils ≥ 1.5 x 10^9/l, Platelets ≥ 100 x 10^9/l; coagulation: INR <1.4 (unless therapeutically anti-coagulated) and/or APPT ratio <1.4.

	3.0 3.0	02/03/2020 3.0 27/07/2020	Information regarding nab-paclitaxel added including: • Rationale for use as alternative • Mechanism of action and toxicities • Supply, storage and labelling • Prescribing and dispensing • Dose modification information • Management of toxicity and hypersensitivity reactions. • Dispensing 2 cycles worth of IMP at PI discretion from cycle 3 of oral IMP only. • Consultations can be done via telephone call. • Urinalysis, Bloods and BP to be done locally (GP/local hospital) for patients on oral IMP if they unable to attend the site. • Postal delivery of oral IMP at PI discretion
	4.0	23/08/2021	• Contact details from Dr Tracie Madden to Dr Ruby Ray.

			• Section 2 Synopsis-Primary outcome definition has been amended to allow for earlier analysis. • Section 5.3 Primary outcome measure has been amended from "4 weeks after stopping cediranib" to "until patient withdraws, dies or has been treated with cediranib for at least 18 weeks" to allow for early analysis. • Section 5.4 has been changed to remove "causally related to treatment" as this is only possible for SAEs and not AEs reported on CRF toxicity pages. Treatment compliance has been amended to clarify the calculation of relative dose intensity. • Section 12.5 Follow up amended to allow for earlier primary analysis. • Section 14.5 has been amended to clarify the analysis populations for primary and secondary endpoints. • Section 15.1.1 Safety analysis has been amended as only SAEs have causality assessed so this will be

			presented separately to all adverse events. A full description of analysis of AEs and SAEs as detailed in the SAP has been added. Analysis of vital signs, ECG and clinical and laboratory parameters has been moved to an additional analysis section as this is not mentioned in the trial objectives or primary, secondary or exploratory outcomes. • Section 15.1.2 Treatment compliance has been amended to match the presentation of treatment compliance in the SAP. • Section 15.2 has been amended to include clinical progression on RECIST forms as progression event. • Section 15.3 & 15.4 has been amended to add patients having cediranib and/or paclitaxel for inclusion in final analysis of primary endpoint. • Section 18 The end of trial definition has been clarified as the date of final data capture for primary analysis.

2 Synopsis

Short title	Evaluation of the safety of CEdiranib in the prevention of Bowel perforation in platinum-resistant Ovarian Cancer
Acronym	CEBOC
Clinical phase	Phase II
Funder and ref.	AstraZeneca (AZ) Reference ESR-15-11304
Trial design	This is a single arm, phase II trial of cediranib 20mg/day with weekly paclitaxel 70mg/m^2/week in patients with recurrent platinum-resistant ovarian cancer and clinical and/or radiological features indicating an increased risk of developing subacute bowel obstruction. The trial has a safety design where the number of participants developing bowel perforation or fistula will be monitored At the point of developing progressive disease (PD), participants cease paclitaxel and have the option of continuing cediranib 20mg/day with olaparib 300mg bd twice daily continuously until further PD occurs.
Trial participants	Progressive, platinum-resistant or refractory, high-grade ovarian, fallopian tube or primary peritoneal cancer with high risk of bowel obstruction.
Planned sample size	30
Planned number of sites	1
Summary inclusion criteria for paclitaxel and cediranib treatment (note there are additional inclusion criteria for patients switching to olaparib)	For full and detailed inclusion criteria see sections: 8.1 inclusion criteria. 1. Histologically confirmed, progressive, platinum-resistant or refractory, high-grade ovarian, fallopian tube or primary peritoneal cancer for which weekly paclitaxel would be a potential treatment option. 2. Aged 16 years or over. 3. Patients who are at risk of bowel obstruction are eligible for the trial. Previous bowel obstruction is permitted providing patients can take

	oral medication and there is no concern about absorption of oral medication. Recto sigmoid involvement is permitted. 4. Adequate haematological function: Hb ≥ 90 g/l, Neutrophils ≥ 1.5 x 10^9/l, Platelets ≥ 100 x 10^9/l; coagulation: INR <1.4 (unless therapeutically anti-coagulated) and/or APPT ratio <1.4. 5. Adequate renal function defined as Glomerular Filtration Rate (GFR) ≥50ml/min and Creatinine clearance ≥50 mL/min using modified Wright or Cockcroft-Gault formula. 6. Adequate liver function: bilirubin ≤ 1.5 x Upper Limit of Normal (ULN), transaminases ≤ 3 x ULN. 7. Previous use of weekly paclitaxel in the platinum-sensitive setting is permitted. 8. Controlled hypertension is permitted. Resting blood pressure (BP) measurements must be; SBP ≤150 mmHg; DBP ≤ 90mmHg and taken in the clinic setting by a medical professional within 2 weeks prior to the scheduled start of treatment with or without anti-hypertensive medication. Adequately controlled BP is permitted on a maximum of three antihypertensive medications. 9. ECOG performance status 0-2 and life expectancy of over 12 weeks. 10. Adequately controlled thyroid function, with no symptoms of thyroid dysfunction. 11. Evaluable disease on CT scan per Response Evaluation Criteria v1.1 (RECIST 1.1). 12. Previous bevacizumab is permitted but patients cannot have been treated with VEGF RTKi previously. 13. Written informed consent. 14. Able to swallow and retain oral medications and without gastrointestinal (GI) illnesses that would preclude absorption of cediranib or olaparib.
Summary exclusion criteria for paclitaxel	For full and detailed exclusion criteria see sections: 8.2 exclusion criteria.

and cediranib treatment (Note that there are additional exclusion criteria for patients switching to olaparib.)	1. Patients with a known hypersensitivity to olaparib or cediranib. 2. Patients with hypersensitivity to paclitaxel who are unable to tolerate nab-paclitaxel as an alternative treatment. 3. Concurrent medical illness that would impact on compliance with the protocol including myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) or with features which suggestive of MDS/AML. 4. Uncontrolled brain metastases or seizures. Central nervous system metastases: i. Symptomatic uncontrolled brain metastases requiring corticosteroid treatment. ii. History of spinal cord compression unless after definitive treatment the patient has clinically stable disease (SD) for at least 28 days prior to starting IMPs Note that in the absence of these features and in an asymptomatic patient, a scan to confirm the absence of brain metastases is not required. 5. Known positivity for Hep B, Hep C or HIV. 6. Resting ECG with QTc > 470msec on 2 or more time points within a 24-hour period or family history of long QT syndrome. 7. Use of known strong or moderate CYP3A inhibitors within two weeks of the start of trial treatment. 8. Use of known strong or moderate CYP3A inducers within 5 weeks of the start of trial treatment for enzalutamide or phenobarbital and within 3 weeks for other agents. 9. Another cancer, which has been active within the previous 5 years, except for adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin and no evidence of recurrence of other malignancy. 10. Patients who are pregnant or lactating. Also, patients who are able to become pregnant unless they agree to use highly effective contraception, or observe true sexual abstinence, for four weeks

	before entering the trial, during the trial and for six months afterwards (see section 8.2 and8.4) for full details). 11. Patients who are planning to receive maintenance bevacizumab. 12. Radiotherapy, surgery or tumour embolization within 28 days before the first dose of cediranib. 13. No additional concurrent anti-cancer therapy is permitted. 14. No cause of malabsorption e.g. uncontrolled diarrhoea or poorly controlled stoma is permitted. 15. Patients who have or have had prior leukoencephalopathy, recent (within the past 6 months) arterial thromboembolic event (MI/CVA within previous 6 months), previous or concurrent fistula, previous or concurrent GI perforation, concurrent intra-abdominal abscess, previous VEGF RTKi or clinically relevant proteinuria, are excluded. 16. Inability to comply with the protocol. 17. Major surgery within two weeks of starting study treatment and patients must have recovered from any effects of any major surgery. 18. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Prior history of other significant impaired cardiac function. 19. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication. 20. Patients with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids. 21. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. 22. Persisting ≥Grade 2 CTCAE toxicity (except alopecia and Grade 2 peripheral neuropathy) from previous anti-cancer treatment(s). 23. No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation.

Treatment duration	**Cediranib and weekly paclitaxel** Participants will receive weekly intravenous (IV) paclitaxel and oral cediranib for six 3-weekly cycles followed by maintenance cediranib until progression. Cediranib will start at cycle 2 or 3 where symptoms of bowel obstruction are prominent. Weekly nab-paclitaxel is a suitable alternative if weekly paclitaxel is contra-indicated due to hypersensitivity. **At the point of developing PD** Eligible participants will receive olaparib 300 mg twice daily and cediranib 20 mg OD orally. The duration of trial treatment may depend on the time until disease progression. It is expected that most participants will receive treatment for approximately 12 months.
Follow-up duration	28 days
Planned trial period	60 months (10 months set-up, 24 months recruitment, 13 months follow-up and 12 months data analysis, publication and study close).
Primary objective	The primary aim of the trial is to determine the safety of combining cediranib with weekly paclitaxel/nab-paclitaxel in women who are at risk of developing malignant bowel obstruction from ovarian cancer; a group of patients for whom bevacizumab would be contra-indicated.
Secondary objectives	The secondary aims are to determine whether cediranib prevents severe bowel obstruction and to determine the toxicities, feasibility and efficacy of the combination of paclitaxel/nab-paclitaxel and cediranib.
Tertiary/Exploratory objectives	Additional aims are to determine the toxicities, Objective Response Rate (ORR) and time to further progression after switching to olaparib/cediranib at first progression.
Primary outcomes	The primary outcome is the number of patients who are free of grade III-V gastrointestinal perforation or fistula, which is causally related to cediranib or the cediranib/olaparib combination, during cediranib treatment until patient withdraws, dies or has been treated with cediranib for at least 18 weeks.
Secondary outcomes	The secondary outcomes are:

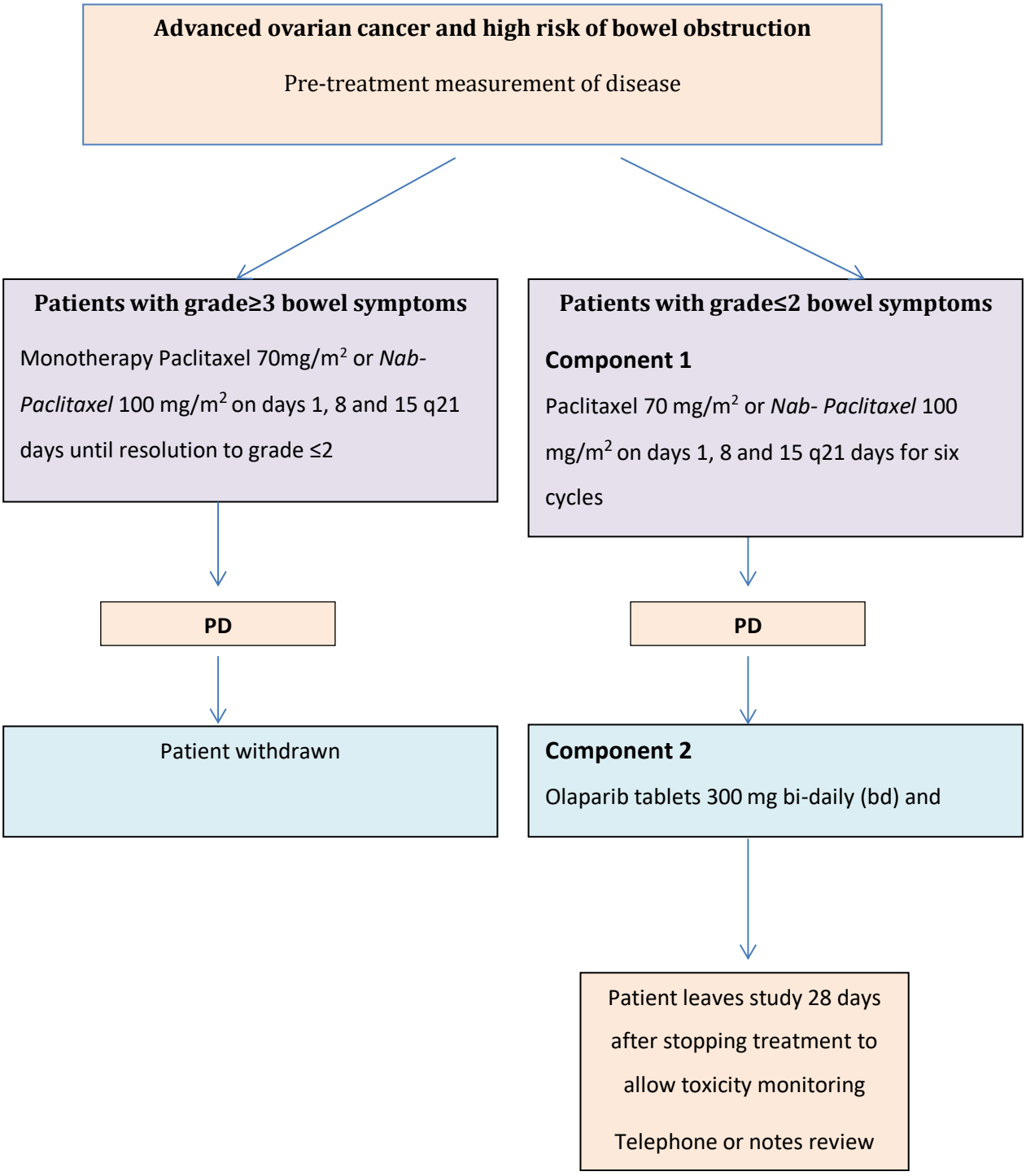
	1) Proportion of participants hospitalised for bowel obstruction. 2) Toxicity excluding gastrointestinal perforation/ fistula. 3) Treatment compliance. 4) ORR within 18 weeks of starting paclitaxel/ nab-paclitaxel. 5) Progression free survival (PFS) to first progression. 6) Overall survival (OS).
Tertiary/Exploratory outcomes	1) Association between prior treatment with bevacizumab and toxicities, ORR, PFS and OS. 2) After switching from cediranib (with or without concurrent paclitaxel/ nab-paclitaxel) to olaparib/cediranib at first point of disease progression: • Toxicities. • Association between BRCA status and toxicities, ORR, PFS and OS. • ORR and time to further progression from the dates of switching to olaparib.

Investigational medicinal products (IMPs)	*Paclitaxel*	*Nab- Paclitaxel*	*Cediranib*	*Olaparib*
Form	Solution for dilution for infusion.	Solution for dilution for infusion.	Tablet	Tablet
Dose	70mg/m^2 on days 1, 8 and 15. Up to 6 cycles will be administered	100 mg/m^2 on days 1, 8 and 15. Up to 6 cycles will be administered	20 mg tablets taken once a day continuously in 21-day cycles until the point of PD. After PD, 20 mg tablets taken once a day continuously in	300 mg taken twice a day, continuously in 21-day cycles after PD in component 1 Note that patients will take olaparib in combination with cediranib

			21-day cycles, in combination with olaparib, until the point of further PD.	(20 mg cediranib tablets taken once a day continuously in 21-day cycles) until further PD.
Route	Intravenous (IV)	Intravenous (IV)	Oral	Oral

Trial summary & schema

3.1 Participant flow diagram



3.2 Trial lay summary

Is it safe to add Cediranib to weekly paclitaxel chemotherapy in women with ovarian cancer who are at risk of developing malignant bowel obstruction?

In the UK, ovarian cancer is the fourth most common cause of female cancer death and the commonest cause of gynaecological cancer death accounting for 4,000 lives a year in the UK. The principal cause of death in ovarian cancer is malignant bowel obstruction. As the disease causes multi-site obstruction of the bowel, surgery is seldom possible and therefore there is a critical need to develop new treatments to stop the development of bowel obstruction as effectively and safely as possible. CEBOC is the first trial that has been developed specifically to address the management of malignant bowel obstruction.

CEBOC aims to take advantage of the additive effects of combining a VEGF inhibitor, cediranib, with an effective chemotherapeutic regimen, weekly paclitaxel or nab-paclitaxel. Subsequently, the patient can continue cediranib with the addition of an additional drug, olaparib at the point of PD. CEBOC will recruit 30 women aged 16 years or older with ovarian cancer, which has placed the patient at risk of developing bowel obstruction.

The main objective of the trial is to determine the safety of combining cediranib with paclitaxel/nab-paclitaxel. Safety will be assessed by monitoring the frequency of two serious adverse events (AEs), bowel perforation and fistula.

The trial will also summarise the side-effects of the treatments and how well the treatment works in terms of controlling the disease and preventing bowel obstruction.

4 Background

Ovarian cancer is the fourth most common cause of female cancer death and the commonest cause of gynaecological cancer death, accounting for 4,000 lives a year in the UK and 22,000 in the United States[1,2]. The most common cause of death is malignant bowel obstruction, which occurs because of tumour physically and neurologically arresting bowel function[3].

New treatment strategies are required to address malignant bowel obstruction, which usually occurs in patients whose disease has become resistant to platinum-based chemotherapy. Several studies have reported higher response rates and increased PFS when a VEGF pathway inhibitor is combined with cytotoxic therapy in the first line[4,5], platinum-sensitive[6,7] and platinum-resistant recurrent disease settings[8]. In the AURELIA study, the addition of the anti-angiogenic, monoclonal anti-VEGF antibody,

bevacizumab, to physician's choice of cytotoxic agent significantly improved PFS. However, this study excluded patients who had received more than three previous regimens of treatment and those with clinical or radiological features of bowel obstruction on the basis that previous data had shown that the administration of bevacizumab to patients with prior bowel surgery, pelvic disease involving the recto sigmoid or symptoms of bowel obstruction would significantly increase the risk of bowel perforation[9], which can be fatal.

The above data demonstrate that there is an unmet need for a VEGF inhibitor that can be safely combined with cytotoxic therapy, which would increase the response rate and PFS in this population. The MITO-11 study demonstrated the safety and potential efficacy of the combination of pazopanib with weekly paclitaxel in platinum resistant disease[11] and we have demonstrated in our in-house trial of cediranib with radiotherapy in colorectal cancer (DREAM trial; manuscript in preparation) that cediranib is effective and safe in the context of significant bowel wall disease, where bevacizumab has been previously reported to induce significant toxicity[12,13]. Taking these findings together, there is a strong rationale to develop a safe VEGF inhibitor-combination regimen in the setting of patients at risk of subacute bowel obstruction from ovarian cancer. Here, we will evaluate the safety and efficacy of the potent VEGF receptor tyrosine kinase inhibitors (RTKi), cediranib, with weekly paclitaxel/nab-paclitaxel in women who are at risk of developing malignant bowel obstruction from ovarian cancer; a population in which bevacizumab is contra-indicated. Any risk to the patient's bowel will be minimized by bringing the abdominal disease under control with weekly paclitaxel /nab-paclitaxel for 1-3 cycles (3-9 weeks) before introducing the combination of paclitaxel/nab-paclitaxel with cediranib.

4.1 Rationale for current trial/Justification of Treatment Options

There is a critical need to develop effective and safe treatment regimens for patients with subacute bowel obstruction from ovarian cancer. Several trials have demonstrated the clinical benefit of adding bevacizumab to cytotoxic therapy in various settings in the disease yet in sub-acute bowel obstruction or in moderately heavily pre-treated patients, the antibody is contra-indicated due to the risk of bowel perforation or fistula.

Several findings suggest that VEGF RTKi are safer than antibodies in the presence of bowel dysfunction while preserving the efficacy advantage of the combination regimen. Here, we will evaluate the safety of the potent VEGF RTKi, cediranib, in combination with weekly paclitaxel/nab-paclitaxel in a cohort

of patients at risk of developing malignant bowel obstruction, for whom bevacizumab is contraindicated.

4.1.1 Rationale for dose and schedule of paclitaxel

Paclitaxel will be administered in CEBOC at 70 mg/m^2/week on days 1, 8 and 15 of a 3-week schedule, where the plan will be for patients to receive 6 cycles of treatment. The treatment is being given on a continuous weekly schedule in the same way that paclitaxel was prescribed in two large randomised trials of paclitaxel with a VEGF inhibitor. In one trial the VEGF inhibitor was the monoclonal anti-VEGF antibody, bevacizumab[14] and in the other, the VEGF receptor tyrosine kinase inhibitor, pazopanib was used[15]. These two trials demonstrated that weekly paclitaxel can be safely and effectively combined with a VEGF inhibitor. However, the pazopanib trial, which involved administration of a VEGF inhibitor of the same class as cediranib, reported that 30% of patients incurred grade 3 or 4 neutropenia yet the investigators had restricted entry to the study to patients who had only received up to 3 previous lines of treatment. In CEBOC, patients can have received any number of previous lines of treatment and therefore to mitigate the risk of neutropenia, the trial involves the prescription of paclitaxel at 70 mg/m^2/week rather than the slightly higher dose used in these two trials. As there is no evidence of a dose-response effect beyond standard doses of paclitaxel[16], the proposed regimen of 70 mg/m^2/week remains a standard of care.

4.1.2 Rationale for use of nab-paclitaxel as alternative

Nab-paclitaxel is a solvent-free, albumin-bound form of paclitaxel. It is indicated for use as an alternative treatment in patients with hypersensitivity to paclitaxel. In the CEBOC trial, if a patient has had a previous hypersensitivity to paclitaxel but is thought to benefit from a weekly taxane chemotherapy, they can be treated with weekly nab-paclitaxel. The dose will be 100 mg/m^2/week on days 1, 8 and 15 of a 3-week schedule, with an aim to plan for 6 cycles of treatment. This is the dose used in the GOG study for treatment of recurrent ovarian cancer with weekly nab-paclitaxel (Robert L. Coleman, 2011) and studies have shown that nab-paclitaxel is safe for use in patients with previous hypersensitivity reactions to paclitaxel. (Kathryn Maurer, 2017)

4.1.3 Rationale for dose of cediranib

The dose of cediranib selected for CEBOC is 20 mg/day, which was biologically and clinically active in early phase clinical trials[17]. Early attempts to combine cediranib with cytotoxic chemotherapy using a dose of the former at 30 mg/day proved intolerable[18] and therefore the standard combination dose of cediranib in recurrent ovarian cancer was 20 mg/day.

Once patients in CEBOC have completed a maximum of 18 weeks of treatment with paclitaxel or nab-paclitaxel, those who have SD or better can continue taking cediranib alone at 20mg/day; again, a dose that was used as maintenance therapy in ICON6[18]. At the point of developing PD in CEBOC patients will need to fulfil another set of eligibility criterion but if they remain eligible, they can then supplement the cediranib with olaparib (see 4.1.3). The reason that the cediranib dose will remain 20 mg/day in this component of CEBOC is because the phase II trial that described the activity of the combination[19] initially involved administration of a dose of cediranib 30 mg/day, but this had to be reduced in 77% of patients to 20 mg/day. Given the amount of previous treatment the patients will have received at this point in CEBOC it is appropriate to use the more tolerable dose of cediranib, namely 20 mg/day.

4.1.4 Rationale for dose of olaparib

In CEBOC, patients who develop PD while taking cediranib and who remain eligible to continue in the trial, will be prescribed olaparib tablets 300 mg bd in addition to cediranib 20 mg/day. The original formulation of olaparib was as 50 mg capsules and the dose of capsules was 400 mg bd. As the capsules only contained 50 mg olaparib, the number of capsules patients had to take was considerable. Because of this, a tablet formulation of olaparib was developed, which resulted in the same exposure to olaparib tablets when 300 mg tablets twice daily were compared with capsules at 400 mg twice daily, yielding similar clinical efficacy and toxicity while reducing the pill burden to four 150 mg tablets per day[20].

The recommended monotherapy tablet dose of 300mg bd has now been evaluated as maintenance therapy in BRCA-mutation associated platinum-sensitive ovarian cancer in a placebo-controlled randomised phase 3 trial[21] where it demonstrated similar efficacy to that reported for the capsule formulation in the initial seminal randomised phase II trial which resulted in EMEA approval for olaparib (Ledermann et al 2012).

A further phase II trial confirmed that the all-tablet cediranib-olaparib combination was associated with toxicities consistent with those observed when olaparib capsules were given in combination with cediranib[22]. This study established two acceptable options for phase II dosing; either cediranib 20 mg OD and olaparib 300 mg twice daily, or cediranib 30 mg OD and olaparib 200 mg twice daily. Based on the earlier combination study showing that a high proportion of cediranib dose reductions were required from a starting dose of 30 mg OD[19], therefore for the purpose of this trial, participants will receive cediranib 20 mg OD and olaparib tablets 300 mg twice daily.

5 Trial objectives/endpoints and outcome measures

5.1 Primary objective

The primary aim of the trial is to determine the safety of combining cediranib 20 mg/day with weekly paclitaxel 70 mg/m^2/week or nab-paclitaxel 100 mg/m^2/week in women who are at risk of developing malignant bowel obstruction from ovarian cancer; a group of patients for whom bevacizumab would be contraindicated.

5.2 Secondary objectives

1) To determine whether cediranib prevents severe bowel obstruction.
2) To determine the toxicities, feasibility and efficacy of the combination of paclitaxel and cediranib or nab-paclitaxel and cediranib.

5.3 Primary outcome measure

The primary outcome is the number of patients who are free of grade III-V gastrointestinal perforation or fistula, which is causally related to cediranib or the cediranib olaparib combination, during cediranib treatment until patient withdraws, dies or has been treated with cediranib for at least 18 weeks..

5.4 Secondary outcomes measures

The secondary outcome measures are:

1) The proportion of participants hospitalised for bowel obstruction.
2) The number of grade III or higher toxicities, excluding gastrointestinal perforation/ fistula as assessed by CTCAE 4.03.

3) Treatment compliance, as assessed by the relative dose intensity of paclitaxel, nab-paclitaxel and cediranib in Component 1; and the relative dose intensity of cediranib and olaparib in Component 2. Total dose delivered and DDI will also be presented.

This will be calculated as (DDI/SDI)×100%, where DDI=Delivered dose intensity and SDI=Standard dose intensity:

DDI=(Delivered total dose, in relevant units)/(actual time to complete chemotherapy with imputation for missed cycles, in days)

Delivered total dose=Total amount of drug actually administered over chemotherapy course

Actual time to complete chemotherapy= Observed number of days between initiation and final receipt of chemotherapy plus expected number of days for missing cycles

SDI= (Standard total dose, in relevant units)/(standard time to complete chemotherapy, in days)

Standard total dose= Total standard amount of drug for administration over chemotherapy course

Standard time to complete chemotherapy= Standard number of days between initiation and final receipt of chemotherapy

4) Investigator-determined ORR assessed by RECIST 1.1 within 18 weeks of starting paclitaxel or nab-paclitaxel.
5) PFS, where PFS is measured as the time from date of registration to date of investigator-assessed objective progression via RECIST v1.1 or death from any cause in the absence of progression.
6) OS defined as the time from date of registration to date of death.

5.5 Separate exploratory objectives and endpoints

The exploratory research outcomes are:

1) The association between prior treatment with bevacizumab and toxicities, ORR, PFS and OS.
2) After switching from cediranib (with or without concurrent paclitaxel or nab-paclitaxel) to olaparib/cediranib at the first point of disease progression:
    a) Grade III or higher toxicities as assessed by CTCAE 4.03.
    b) Association between BRCA status and grade III or higher toxicities, ORR, PFS and OS.
    c) ORR and time to further progression from the date of starting olaparib.

6 Trial design and setting

This is a single arm, UK, phase II trial of cediranib 20 mg od with paclitaxel 70 mg/m^2/week or nab-paclitaxel 100 mg/m^2/week patients with recurrent platinum-resistant ovarian cancer and clinical and/or radiological features indicating an increased risk of developing subacute bowel obstruction. Participants will receive paclitaxel or nab-paclitaxel for 6 cycles (21-day cycle) with, cediranib introduced between 0-3 cycles if bowel symptoms have stabilised. Following the 6th cycle of paclitaxel or nab-paclitaxel, participants can continue to take single agent cediranib 20 mg od until PD occurs. Nab-paclitaxel is considered a suitable alternative to paclitaxel if the patient has had previous hypersensitivity reactions to paclitaxel.

At the point of developing PD, paclitaxel or nab-paclitaxel will be stopped. If the participant has not commenced cediranib they will be withdrawn from the trial. Participants receiving cediranib will be screened for eligibility to continue cediranib 20 mg od with the addition of olaparib 300 mg twice daily. We expect to reach our enrolment target, of 30 patients, within 24 months of trial opening and all patients recruited will be followed up for at least 13 months following registration, or until 28 days after withdrawing from trial treatment. The end of the trial will be 28 days after the last treatment visit.

Data will be collected on paper based CRFs and submitted to the CTR through the postal system.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

1) The risk to participant safety in relation to the trial intervention compares to that of standard care.
2) All other risks related to the design and methods of the trial (including risks to the participant rights and rights as well as the reliability of the results.

This trial has been categorised as a Risk Type C, where the level of risk is somewhat higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial

Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 22.1).

7 Site and Investigator selection

This trial will be a single site study, conducted at The Christie NHS Foundation Trust the UK. The trust will be required to complete a registration/feasibility form to confirm that they have adequate resources and experience to conduct the trial. All patients will be identified and recruited at The Christie NHS Foundation Trust. The TM will liaise with the trust to ensure the trial is opened to recruitment in accordance with the Sponsor procedures for site activation.

The Christie NHS Foundation Trust will:

- Have an identified PI.
- Be provided with protocol specific training prior to being activated for recruitment.
- Be supplied with a local document package in line with HRA guidance (http://www.hra.nhs.uk/resources/hra-approval-nhs-organisation-guidance/). For sites in England this package will be provided simultaneously to both the study delivery team and the research management team.
- Be provided with copies of the REC, HRA and competent authority approvals for the trial. Note that the approval process includes granting favourable opinion of the host care organisation/PI.
- Have local Trust R&D approval by confirmation of site capability and capacity to undertake the study.
- Execute a signed trial site agreement and other required agreements.
- Have a current Curriculum Vitae and GCP training certificate of the PI.
- Complete a Site Delegation Log and Roles and Responsibilities document. It is the responsibility of the PI to ensure only trained and appropriately delegated staff work on the trial.
- Be provided with an ISF which will be maintained and stored securely.
- Be supplied with a trial set-up pack containing paper CRFs which will be stored securely.
- Provide full contact details for all host care organisation personnel involved, indicating the preferred contact.
- Provide a set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses.
- Return a copy of the Self-Evident Correction Log signed by the PI.

- Provide Pharmacy confirmation that they have received the first shipment of IMP prior to the site being activated for recruitment.

The documents must be in place and copies sent to the CEBOC Trial email account (see contact details on page 4).

Site initiation will be by attendance at a national CEBOC launch meeting, or by teleconference or a meeting at site if attendance of key personnel at a launch meeting is unfeasible.

Once a site is ready to open for recruitment this will be confirmed in writing to them via an email of authorisation sent by the TM. This email must be filed in the Site File.

8 Participant selection

Participants are eligible for the trial if they meet all the following inclusion criteria and none of the exclusion criteria apply. The eligibility decision for each participant will be made by a medically qualified doctor (or their medically qualified delegate as documented on the Site Delegation Log) and documented in the CRF and medical notes. All queries about participant eligibility should be directed to the TM before registration. Protocol waivers **are not** permitted.

8.1 Inclusion criteria: Prior to paclitaxel/*nab-paclitaxel* and cediranib (Component 1)

1) Histologically confirmed, progressive, platinum-resistant or refractory, high-grade ovarian, fallopian tube or primary peritoneal cancer for which weekly paclitaxel or nab-paclitaxel would be a potential treatment option.
2) Aged 16 years or over.
3) Patients who are at risk of bowel obstruction are eligible for the trial. Features that are compatible with this diagnosis include increasing abdominal pain and swelling, borborygmi, change in bowel habit, extensive serosal disease or dilated or tethered bowel on radiological investigation. It is anticipated that one or more of these should be present in eligible patients. Previous bowel obstruction is permitted providing patients can take oral medication and there is no concern about absorption of oral medication. Recto sigmoid involvement is permitted.
4) Adequate haematological function Hb ≥ 90 g/l, Neutrophils ≥ 1.5 x 10^9/l, Platelets ≥ 100 x 10^9/l; coagulation: INR <1.4 (unless therapeutically anti-coagulated) and/or APPT ratio <1.4.
5) Adequate renal function defined as GFR ≥50 ml/min and Creatinine clearance ≥50 mL/min using modified Wright or Cockcroft-Gault formula.
6) Adequate liver function: bilirubin ≤ 1.5 x ULN, transaminases ≤ 3 x ULN.

7) The previous use of weekly paclitaxel or nab-paclitaxel in the platinum-sensitive setting is permitted.
8) Controlled hypertension permitted. Patients must have a blood pressure (BP) of ≤ Systolic BP (SBP) 150/ ≤ Diastolic BP (DBP) 90 mmHg, with or without anti-hypertensive medication. BP measurements must be taken in the clinic setting by a medical professional within 2 weeks prior to starting study treatment. A maximum of 3 anti-hypertensive medications are permitted and it is strongly recommended that patients who are on 3 anti-hypertensive medications be followed by a cardiologist or a primary care physician for management of BP while on study.
9) ECOG performance status 0-2 and life expectancy of over 12 weeks.
10) Adequately controlled thyroid function, with no symptoms of thyroid dysfunction.
11) Evaluable disease on CT scan per RECIST v1.1.
12) Previous bevacizumab is permitted but patients cannot have been treated with VEGF RTKi previously.
13) Ability to provide written informed consent.
14) Able to swallow and retain oral medications and without gastrointestinal (GI) illnesses that would preclude absorption of cediranib or olaparib.

8.2 Exclusion criteria: Prior to paclitaxel/*nab-paclitaxel* and cediranib (Component 1)

1) Patients with a known hypersensitivity to olaparib or cediranib or any of the excipients of the products.
2) Patients with hypersensitivity to paclitaxel who are unable to tolerate nab-paclitaxel as an alternative treatment.
3) Concurrent medical illness that would impact on compliance with the protocol including myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) or with features which suggestive of MDS/AML.
4) Uncontrolled brain metastases or seizures. A scan to confirm the absence of brain metastases is not required. Central nervous system metastases:
    - Symptomatic uncontrolled brain metastases requiring corticosteroid treatment.
    - History of spinal cord compression unless after definitive treatment the patient has clinically SD for at least 28 days prior to starting IMPs. In the absence of these features and in an asymptomatic patient a scan to confirm the absence of brain metastases is not required.

5) Known positivity for Hep B, Hep C or HIV.
6) Resting ECG with QTc > 470 msec on 2 or more time points within a 24- hour period or family history of long QT syndrome.
7) Concomitant use of known strong CYP3A4/5 inhibitors such as such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. Concomitant use of inducers or inhibitors (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) is also excluded. The required washout period prior to starting olaparib is 2 weeks.
8) Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
9) Another cancer, which has been active within the previous 5 years, except for adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin and no evidence of recurrence of other malignancy.
10) Pregnant or lactating. Pregnancy status in women of childbearing potential will be confirmed via a serum or urine pregnancy test prior to registration, monthly during the treatment period, and at the end of treatment assessment. In addition, women of childbearing potential MUST be willing to ensure they use effective contraception for four weeks before entering the trial, throughout the treatment period and for six months following the end of treatment. Acceptable methods of contraception are:
    i. true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant
    ii. a combination of male condom plus one of:
        - vasectomised sexual partner, with participant assurance that partner received post-vasectomy confirmation of azoospermia.
        - Tubal occlusion.
        - Intrauterine device provided coils are copper-banded.
        - Etonogestrel implants (e.g., Implanon®, Norplant®.
        - Normal and low dose combined oral pills.
        - Hormonal shot or injection (e.g., Depo-Provera).
        - Intrauterine system device (e.g., levonorgestrel-releasing intrauterine system -Mirena®).

- Norelgestromin/ethinyl estradiol transdermal system.
- Intravaginal device (e.g., ethinyl estradiol and etonogestrel).
- Cerazette (desogestrel). Cerazette is currently the only highly efficacious progesterone-based pill.

11) Patients who are planning to receive maintenance bevacizumab.
12) Radiotherapy, surgery or tumour embolization within 28 days before the first dose of cediranib.
13) No additional concurrent anti-cancer therapy is permitted.
14) No cause of malabsorption e.g. uncontrolled diarrhoea or poorly controlled stoma is permitted.
15) Patients who have or have had prior leukoencephalopathy, recent (within the past 6 months) arterial thromboembolic event (MI/CVA within previous 6 months), previous or concurrent fistula, previous or concurrent GI perforation, concurrent intra-abdominal abscess, previous VEGF RTKi or clinically relevant proteinuria, are excluded.
16) Inability to comply with the protocol.
17) Major surgery within two weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
18) 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, unstable angina, recent (within 6 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, resting ECG with clinically significant abnormal findings, NYHA grade III/IV cardiac failure, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent. Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines, for patients with the following risk factors:
    a) Prior treatment with anthracyclines– except liposomal doxorubicin, which is permitted.
    b) Prior treatment with trastuzumab.
    c) Prior central thoracic RT, including exposure of heart to therapeutic doses of ionizing RT.
    d) History of myocardial infarction within 6-12 months prior to start of IMPs.
    e) Prior history of other significant impaired cardiac function.

19) Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
20) Patients with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids
21) Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment.
22) Persisting ≥Grade 2 CTCAE toxicity (except alopecia and Grade 2 peripheral neuropathy) from previous anti-cancer treatment(s).
23) Prior allogeneic bone marrow transplant or double umbilical cord blood transplantation.

8.3 Inclusion criteria: Prior to cediranib and olaparib (Component 2)

1) Radiological evidence of PD that is evaluable per RECIST v1.1.
2) Adequate haematological function: Hb ≥ 90 g/l, Neutrophils ≥ 1.5 x 10^9/l, Platelets ≥ 100 x 10^9/l; coagulation: INR <1.4 (unless therapeutically anti-coagulated) and/or APPT ratio <1.4.
3) Adequate renal function defined as GFR ≥50 ml/min and Creatinine clearance ≥50 mL/min using modified Wright or Cockcroft-Gault formula.
4) Adequate liver function: bilirubin ≤1.5xULN, transaminases≤3xULN.
5) Controlled hypertension permitted. Patients must have a blood pressure (BP) of ≤ SBP:150/ DBP 90 mmHg, with or without anti-hypertensive medication. BP measurements must be taken in the clinic setting by a medical professional within 2 weeks prior to starting study. A maximum of 3 anti-hypertensive medications are permitted and it is strongly recommended that patients who are on 3 anti-hypertensive medications be followed by a cardiologist or a primary care physician for management of BP while on study.
6) ECOG performance status 0-2 and life expectancy of over 12 weeks.
7) Adequately controlled thyroid function, with no symptoms of thyroid dysfunction.
8) No contra-indications to receive cediranib or olaparib.
9) Able to swallow and retain oral medications and without gastrointestinal (GI) illnesses that would preclude absorption of cediranib or olaparib.

8.4 Exclusion criteria: Prior to cediranib and olaparib (Component 2)

1) Patients with a known hypersensitivity to olaparib, cediranib or any of the excipients of the products.

2) Exclude cytotoxic therapy within 4 weeks of starting olaparib.
3) Concurrent medical illness that would impact on compliance with the protocol including AML and MDS.
4) Uncontrolled brain metastases or seizures. A scan to confirm the absence of brain metastases is not required. Central nervous system metastases:
   a. Symptomatic uncontrolled brain metastases requiring corticosteroid treatment.
   b. History of spinal cord compression unless after definitive treatment the patient has clinically SD for at least 28 days prior to starting IMPs. In the absence of these features and in an asymptomatic patient a scan to confirm the absence of brain metastases is not required.
5) Known positivity for Hep B, Hep C or HIV.
6) Resting ECG with QTc > 470msec on 2 or more time points within a 24-hour period or family history of long QT syndrome.
7) Concomitant use of known strong CYP3A4/5 inhibitors such as such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. Concomitant use of inducers or inhibitors (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) is also excluded. The required washout period prior to starting olaparib is 2 weeks.
8) Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
9) Pregnant or lactating. Pregnancy status in WOCP will be confirmed via a serum or urine pregnancy test prior to registration, monthly during the treatment period, and at the end of treatment assessment. In addition, women of childbearing potential MUST be willing to ensure they use effective contraception for four weeks before entering the trial, throughout the treatment period and for six months following the end of treatment. Acceptable methods of contraception are:
   i. true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant).
   ii. a combination of male condom plus one of:
      - vasectomised sexual partner, with participant assurance that partner received post-vasectomy confirmation of azoospermia.
      - Tubal occlusion.

- Intrauterine device provided coils are copper-banded.
- Etonogestrel implants (e.g., Implanon®, Norplant®).
- Normal and low dose combined oral pills.
- Hormonal shot or injection (e.g., Depo-Provera).
- Intrauterine system device (e.g., levonorgestrel-releasing intrauterine system - Mirena®).
- Norelgestromin/ethinyl estradiol transdermal system.
- Intravaginal device (e.g., ethinyl estradiol and etonogestrel).
- Cerazette (desogestrel). Cerazette is currently the only highly efficacious progesterone-based pill.

10) Patients who are planning to receive maintenance bevacizumab.
11) Radiotherapy, surgery or tumour embolization within 28 days before the first dose of cediranib.
12) No cause of malabsorption e.g. uncontrolled diarrhoea or poorly controlled stoma is permitted.
13) Patients who have or have had prior leukoencephalopathy, recent (within the past 6 months) arterial thromboembolic event (MI/CVA within previous 6 months), previous or concurrent fistula, previous or concurrent GI perforation, concurrent intra-abdominal abscess, previous VEGF RTKi or clinically relevant proteinuria, are excluded.
14) Inability to comply with the protocol.
15) Major surgery within six 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, unstable angina, recent (within 6 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, resting ECG with clinically significant abnormal findings, NYHA grade III/IV cardiac failure, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent. Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines, for patients with the following risk factors:
    a) Prior treatment with anthracyclines – except liposomal doxorubicin, which is permitted.
    b) Prior treatment with trastuzumab.

c) Prior central thoracic RT, including exposure of heart to therapeutic doses of ionizing RT.

d) History of myocardial infarction within 6-12 months prior to start of IMPs.

e) Prior history of other significant impaired cardiac function.

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

18) Persisting ≥ Grade 2 CTCAE toxicity (except alopecia and Grade 2 peripheral neuropathy) from previous anti-cancer treatment(s).

19) No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation.

9 Recruitment, Screening and registration

9.1 Participant identification

Potential participants will be under the care of a consultant who specialises in the treatment of ovarian cancer. Once a participant has been identified as potentially eligible to participate, the opportunity will be discussed with the participant and she will be given a copy of the Participant Information Sheet (PIS) and Informed Consent Form (ICF) The patient will be given adequate time to consider the study and given the opportunity to ask further questions.

No sites will be opened as a Participant Identifying Centre. The trial will not be promoted through posters. Information about the trial may appear on websites, but the purpose of these sites is to provide information and not to promote the study to potential participants. If the CTR or University of Manchester is contacted directly by a potential participant, then they will be asked to discuss the trial with their consultant.

9.2 Screening logs

A screening log of all patients who were considered for potential participation in the trial will be kept by each site. This log will record whether the person was considered eligible based on their medical notes, whether they were approached, and whether they consented. A screening log enables any biases from differential recruitment to be detected.

Copies of completed screening logs should be sent to the CEBOC@cardiff.ac.uk as a minimum once every three months. Note that all identifiable information must be removed/obscured from screening logs prior to them being sent to the CTR.

9.3 Recruitment rates

A total of 30 participants will be recruited at an expected rate of 1-2 per month.

9.4 Informed consent

Consent will be taken by a member of the trial team who is GCP trained, suitably qualified and experienced and who has been delegated by the PI to undertake this activity. The participant's written informed consent must be obtained using the ICF, which follows the PIS.

The participant will be given enough time (a minimum of 24 hours) after the initial invitation to participate before commencing the consent process. The participant should also have opportunity to question the PI, their GP or other independent parties to decide whether they will participate in the trial. A contact number should be given to the participant should they wish to discuss any aspect of the trial. The participant must personally sign and date the current approved version of the ICF before any trial specific procedures are performed.

Only when written informed consent has been obtained from the participant, and they have been randomised into the trial, will they be considered a trial participant.

One copy of the ICF will be given to the participant, the original copy will be kept in the ISF, and a further copy will be kept with participant's hospital notes.

It will be clearly stated to the participant that they are free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. After the patient, has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the patient. However, the treatment given and reason for doing so will be recorded and the patient will remain within the trial for follow-up and data analysis.

New safety information may necessitate changes to the PIS and ICF. In this event, it may be necessary to ask some, or all, participants to decide whether to re-consent or withdraw from the trial. Decisions on whether, and which, patients need to re-consent will be made by the TM and CI and documented in the TMF. The TM will communicate the timelines for the re-consent process to be completed. Some patients, for example those who are no longer receiving the IMP concerned, may not need to re-consent but should be informed of the new information as required. The TM will communicate local requirements to participating sites and initiate a process to track progress.

9.5 Registration

Participants will be registered to the trial after confirmation of eligibility and written informed consent has been obtained, and prior to any trial specific procedures (including screening tests) being carried out. The eligibility decision for each participant made by a medically qualified doctor (or their medically qualified delegate as documented on the Site Delegation Log) will be documented in the CRF and medical notes prior to patient registration. All queries about participant eligibility should be directed to the TM before registration. Protocol waivers are not permitted.

Participant registration will be performed by the participant's nurse or doctor via email to CEBOC@cardiff.ac.uk.

The registration procedure will be fully documented, reviewed, tested and approved prior to the start of the study.

The total number of patients recruited will be 30.

The following information will be required to register a patient:

1) The name of person registering the patient.
2) Confirmation of the participant's eligibility.
3) The participant's initials and date of birth.

Following registration, a confirmation email containing details of the allocated Trial ID will be sent to the recruiting site and specified members of the trial team will be notified. From this point forward the Trial ID should be used in all correspondence and on all relevant trial documentation.

Registration details and enquires must be directed to the trial specific email account CEBOC@cardiff.ac.uk

Following registration, participants will be issued with a Participant Trial Card, completed with the name of the local PI and the out of hours contact details in the event of an emergency. A Participant Diary will also be supplied to monitor IMP and protocol compliance (see section 22).

9.6 Confirmation of eligibility for patients switching to olaparib and cediranib

Patients who have evidence of PD (as per RECIST v1.1) during cediranib treatment may be eligible to switch to cediranib and olaparib treatment.

A second eligibility screen is required to ensure the participant continues to meet all the inclusion listed in section 8.3 and none of the exclusion criteria listed in section 8.4. The eligibility decision for each participant made by a medically qualified doctor (or their medically qualified delegate as documented on the Site Delegation Log) will be documented in the confirmation of eligibility prior to olaparib treatment CRF and medical notes prior to the participant starting olaparib treatment.

All queries about participant eligibility, to switch to olaparib, will be directed to the CI via the TM. Protocol waivers are not permitted. On confirmation of participant eligibility and prior to the start of olaparib treatment, please email CEBOC@cardiff.ac.uk with the following information:

1) Participant Trial ID.
2) Confirmation of eligibility.
3) Date of decision to switch.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. In the CEBOC trial these aspects will be:

- Withdrawal of trial treatment.
- Withdrawal from follow-up assessments.
- Complete withdrawal from data collection.
- Withdrawal of permission to use data already collected.

*For effective safety monitoring, participants cannot withdraw from data collection or follow-up, without also withdrawing from all trial treatment.

Participants may choose to withdraw consent verbally or in writing, and this will be documented in the participant's medical notes. If a participant withdraws consent for participation it is the responsibility of the PI to ensure the participant's withdrawal is documented and implemented.

If, during the trial, the participant loses the mental capacity to give continuing consent then the trial treatments will be stopped, and the person will be treated per local standard NHS practice.

The PI may withdraw a participant from the trial for any of, the following reasons:

- Intolerance to treatment (including toxicities and SAEs).
- Evidence of radiological disease progression based on RECIST v1.1 (only if the participant is not being considered for further cediranib and olaparib treatment as part of the trial).
- Participant choice.
- PI's clinical judgement that withdrawal is in best interest of participant.
- Symptomatic deterioration including participants who experience rapid deterioration before completion of 4 weeks of protocol treatment.
- Sponsor's decision to terminate the trial.
- Pregnancy in the participant.
- Incorrect enrolment.
- Participant lost to follow-up.
- Participant is persistently non-compliant with the trial treatment.
- Participant loses mental capacity to give continuing consent.

All the results of the evaluations and observations, together with the reason for withdrawal from the trial (if known), must be recorded in the patient's medical notes and in the CRF.
Participants who are withdrawn from the treatment due to Adverse Events (AEs) (clinical or laboratory), and have consented to be followed up, will be treated and followed per accepted standard NHS medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF and on the SAE report form where applicable until resolution. Then the patient will be withdrawn from the trial.

If a withdrawn participant is due to start a new therapeutic intervention, the end of treatment assessment should be completed before starting the new therapy.

Participants who have withdrawn from the trial will be followed up for up to 28 days after the last dose of IMP for monitoring of AEs. Participants will only be withdrawn from further follow-up if the participant explicitly states that she does not wish to be followed up further in the trial; if the participant dies, or the end of the trial has been reached. If the participant disease progresses in either Component 1 or Component 2, this is not classed as a withdrawal.

In all instances, a withdrawal form will be completed for participants who consent and subsequently withdraw. The withdrawal form will be completed by the participant or a member of their clinical care team using information provided by the participant. The withdrawal form will be emailed to the Data Manager (DM) via CEBOC@cardiff.ac.uk. The DM will email the recruiting centre to confirm participant withdrawal.

All queries relating to potential withdrawal of a participant will be forwarded to: CEBOC@cardiff.ac.uk.

10.2 Lost to follow up

Participants who withdraw from the trial or cease to attend trial visits prior to the end of the follow-up period will be classed as lost to follow up if we do not have confirmation of PD or death. Every effort will be made to obtain follow-up information on these participants, unless they have completely withdrawn from the trial.

Participants who miss a scheduled visit will be contacted by the local research team and asked to make an appointment to be seen at the next available clinic. If the participant declines or cannot be contacted, the local research team will inform their GP.

If the participant is alive but not compliant with trial medication or the visit schedule, the minimum information we will aim to collect is date of PD, date of death and SAE data. Participants lost to follow up will not be replaced.

11 Trial Intervention

11.1 Treatment(s)

11.1.1 Paclitaxel

Paclitaxel is an antimicrotubule cytotoxic drug that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. It has a Marketing

Authorisation (MA) in the European Union (EU) for the treatment of breast, advanced non-small cell lung cancers, AIDS-related Kaposi's sarcoma and ovarian cancer (either as initial therapy in combination with platinum-containing medicines, cisplatin, or as a second-line treatment when other platinum-containing treatments have failed).

The administration of paclitaxel on a weekly schedule is standard clinical practice for the treatment of recurrent ovarian, breast and endometrial cancers. The site should use the current SmPC for the brand of paclitaxel they use to guide the clinical management of participants receiving paclitaxel. In CEBOC, the use of paclitaxel in combination with cediranib and/or olaparib, is outside the MA and meets the definition of an IMP in accordance with Article 2 of Directive 2001/20/EC.

11.1.2 Nab-paclitaxel

Nab-paclitaxel is paclitaxel, which is bound to nanoparticles of albumin. The albumin binds reversibly in order to transport paclitaxel to target cells where the albumin binds to the protein Secreted Protein Acidic Rich in Cysteine (SPARC). In theory this leads to enhanced accumulation of paclitaxel in the target cell, and when it reaches its target, it acts in the same way as paclitaxel does. This avoids the use of Cremophor EL, which is the solvent in paclitaxel thought to cause most hypersensitivity reactions. Published case reports in ovarian cancer have shown that patients with previous hypersensitivity reactions to paclitaxel can be successfully treated with nab-paclitaxel with no further reactions and with disease response. (Kathryn Maurer, 2017)

Nab-paclitaxel has a MA for use in the EU for metastatic breast cancer, metastatic adenocarcinoma and non-small cell lung cancer. In CEBOC, the use of nab- paclitaxel in combination with cediranib and/or olaparib, is outside the MA and meets the definition of an IMP in accordance with Article 2 of Directive 2001/20/EC.

11.1.3 Cediranib

Cediranib is an orally bioavailable VEGF-R1, -R2 and R3 tyrosine kinase inhibitor. Recent data from ICON6 have shown that the drug improves PFS with a trend towards improved OS in recurrent platinum-sensitive ovarian cancer[15]. Currently the drug does not have MA for use in ovarian cancer. Cediranib (AZD2171) is a potent small molecule VEGF RTKi of all three VEGF receptors (VEGFR-1, -2 and -3) at nano molar concentrations. Inhibition of VEGF signalling leads to the inhibition of

angiogenesis, lymph angiogenesis, neovascular survival and vascular permeability. Cediranib has additional activity against stem cell factor receptor (c-kit) tyrosine kinase inhibiting this kinase with a similar potency to that at which it inhibits VEGFRs. Cediranib is less active versus platelet-derived growth factor receptor (PDGFR) tyrosine kinases, and inactive against other kinases tested.
Cediranib inhibited the growth of tumours in preclinical models in a dose-dependent manner. At doses that reduce tumour growth VEGFR-2 and c-kit were inhibited, but only partial inhibition of PDGFR was observed. Anti-tumour activity was associated with a reduction in micro-vessel density and changes in vascular permeability. Cediranib reduced ascites accumulation in pre-clinical models and in several models also inhibited metastatic dissemination, also blocking VEGFR-3 inhibited lymph angiogenesis. Collectively, these changes indicate that cediranib limits tumour growth, metastases and microvascular permeability. Following OD dosing with 20 mg cediranib, the unbound minimum steady-state plasma concentration (Css, min) was approximately 5-fold greater than the human umbilical vein endothelial cell proliferation inhibitory concentration 50% (IC50) reported in non-clinical studies (Wedge et al 2005).

At a clinical dose of 20 mg in patients, a small increase in DBP and SBP is expected; a significant reduction in serum soluble VEGFR-2 was observed; and a decrease in tumour vessel permeability and vascularity in liver lesions, as measured by dynamic contrast enhanced magnetic resonance imaging, was detected.

11.1.4 Olaparib

Olaparib (Lynparza™) has a MA for the maintenance treatment of epithelial ovarian cancer after response to platinum-based chemotherapy in patients with germline BRCA mutations. In CEBOC, the use of olaparib is outside of the MA and meets the definition of an IMP in accordance with Article 2 of Directive 2001/20/EC.

Olaparib is a potent inhibitor of human poly (ADP ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3). PARP enzymes are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto modifies itself and dissociates from the DNA to facilitate access for base excision repair enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this leads to DNA double strand breaks

(DSBs) when replication forks meet the PARP DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional BRCA1 and 2 genes, is effective at repairing these DNA double strand breaks. In the absence of functional BRCA1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error prone pathways are activated, such as the non-homologous end-joining pathway, leading to increased genomic instability. After several rounds of replication, genomic instability can reach intolerable levels resulting in cancer cell death, as cancer cells have a high DNA damage load relative to normal cells. In BRCA-deficient in vivo models, olaparib given after platinum treatment resulted in a delay in tumour progression and an increase in OS compared to platinum treatment alone; an effect that was corroborated in patients with confirmed deleterious or suspected deleterious BRCA mutation (i.e., a mutation that disrupts normal gene function) in either the germline or the tumour (detected using an appropriately validated test).

Following oral administration of olaparib via the tablet formulation, absorption is rapid. Co-administration of food slows the rate of absorption (tmax delayed by 2.5 hours and Cmax reduced by 20 %). However, food did not significantly affect the AUC. Therefore, olaparib can be taken without regard to food (exceptions may be required when taken with cediranib, see section 11.4.4). Note that this advice differs from the advice with the marketed capsule formulation which should not be taken with food.

CYP3A4 is the enzyme primarily responsible for the metabolism of olaparib. Olaparib can be administered in patients with mild renal impairment (creatinine clearance ≥ 51 ml/min). There are limited data in patients with moderate impairment (creatinine clearance ≤ 50 ml/min) or severe impairment (creatinine clearance ≤ 30 ml/min). Olaparib is not recommended for use in patients with hepatic impairment (serum bilirubin > 1.5 x ULN). For more information, please see section 11.10.2.3.

11.2 Treatment supply and storage

11.2.1 Supply

11.2.2 Paclitaxel and Nab-paclitaxel

Paclitaxel and nab-paclitaxel are commercially available and should be sourced locally as per standard practice at the investigator site using products that have a UK or EU license. Refer to SmPC for further information. As the site may use different brands or manufacturers for these drugs, the site is

responsible for placing the most recent SmPC in the pharmacy folder or a file note that references an electronic source.

Descriptive information for paclitaxel and nab-paclitaxel can be found in the package insert. Study treatment with these drugs should be administered according to the institutional standards at the site. Both paclitaxel and nab-paclitaxel will be used and stored as detailed on the product label and according to manufacturer's instructions. There will be no re-imbursement to sites for these drugs.

11.2.2.1 Olaparib and cediranib

Olaparib and cediranib (table 2) will be supplied by AstraZeneca Pharmaceuticals Ltd. As this is a single site study conducted at The Christie Hospital NHS Foundation Trust the site pharmacy will conduct the labelling under regulation 37 exemptions from The Medicines for Human Use (Clinical Trials) Regulations 2004. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling.
Upon registration of the patients, the TM will inform the participating centre pharmacist and research team the participant trial number to enable the IMPs to be dispensed.

Investigational product	Dosage form and strength	Manufacturer
Olaparib (AZD2281)	100 and 150 mg tablets	AbbVie Deutschland GmbH &co
Cediranib (AZD2171)	15 and 20 mg tablets	AZ Ltd

Table 1: Olaparib and cediranib formulation

Cediranib and olaparib received by the site pharmacy must be acknowledged on receipt of the shipment and recorded in the Drug Inventory Log. Cediranib and olaparib will be temperature monitored during transit and the conditions and integrity of the trial IMP (including confirmation that the IMP remained within the acceptable temperature range) will be recorded. A copy of the acknowledgment will be faxed/emailed to CTR TM with a copy of the accountability log. A running balance will be kept, and any discrepancies will be reported to the TM at CTR immediately. The IMP dispensed to participants enrolled in the trial must be documented in the Accountability Log as well as returned bottles of IMP. The detailed description of the IMP management will be detailed in the IMP management plan. IMPs destruction should be reported to TM for authorisation via the Sponsor. All IMP destruction will be documented, and a copy of the destruction certificate should be stored in the Pharmacy Site File and made available to trial monitor during monitoring visits.

An order to resupply the IMP will be emailed or faxed to the distributor at agreed intervals to maintain local stock levels. A minimum of 10 business days' notice is required for a shipment of the trial IMP to arrive at a participating site pharmacy. The site Pharmacy team should liaise with TM to ensure adequate IMP levels are kept on site for the number of patients enrolled.

11.2.3 Storage

11.2.3.1 Paclitaxel and Nab-paclitaxel

Paclitaxel and nab-paclitaxel will be dispensed from standard hospital stock and will be stored according to the standard requirements for paclitaxel and with the pharmacy's local procedures for temperature monitoring.

11.2.3.2 Olaparib and Cediranib

The site pharmacy will ensure that olaparib and cediranib will be kept in their original containers and stored in a secured area below 30°C (degrees Celsius), in accordance with applicable regulatory requirements.

A temperature log will be used to record the temperature of the storage area. Temperature excursions , outside the permissible range listed in the clinical supply packaging, are to be reported immediately to the TM upon detection via a Drug Quality Form. Decisions will be communicated to the Pharmacy and documented in the Drug Quality Form and TMF. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility.

11.3 Treatment prescribing and dispensing

Upon registration of the participants, the CTR will inform the participating centre pharmacist and research team of the participant allocation via email. The email does not allocate pack numbers. Pharmacy will receive trial specific prescriptions, signed by a delegated member of the research team, for each participant per cycle, with additional prescriptions if dose-reductions are required mid-cycle. Pharmacy will select the appropriate IMP(s) which will then be dispensed in accordance with the prescription, and Pharmacy will ensure the required accountability forms in the PSF are completed.

A maximum of 2 months' worth of oral IMP can be dispensed at a visit if the participant is unable to attend site as required from cycle 3 of oral IMP onwards only. Cycle 1 and 2 of oral IMP must

continue monthly dispensing to allow Investigators to assess whether the patient is tolerating treatment well and gaining clinical benefit. Confirmation that a patient is fit for treatment must be assessed by the clinician using the assessments at the protocol defined timepoints before patients are given the go-ahead to continue with the next cycle.

Postal or delivery via next day service such as courier or Royal Mail Special Delivery is permitted at PI discretion if patient cannot attend a trial site and is being monitored by telephone assessment. The participant must consent verbally (and this should be documented in their notes) to providing contact details for shipping purposes. A follow-up phone call should be used to confirm they have received the oral IMP.

11.4 Dosing schedule

11.4.1 Paclitaxel

Paclitaxel will be administered at a dose of 70mg/m^2 on days 1, 8 and 15 of a 21-day cycle for a maximum of 6 cycles.

Before each paclitaxel infusion, the results from the blood tests must be checked to ensure that treatment can be given. The infusion should only be given if all the required parameters are met. Table 2 shows the required blood values and the action to be taken if any parameter is not met. Treatment decisions should be taken as recently as possible – it is expected that is most cases this will be up to 2 days prior to the planned treatment administration, though up to 4 days is permitted where this is essential (for example where the infusion is immediately after a bank holiday weekend) and if allowed by local procedures.

If the participant is unable or unsuitable to receive paclitaxel on the planned days due to illness or missed visit, then the planned treatment was for:

- Day 1: Treatment is deferred until the following week.
- Day 8 or 15: Treatment is given within 3 days of the scheduled date. If this is not possible, treatment is omitted, and next treatment is given in accordance to original timeline.

Day	Required blood parameters	Action if parameter is not met
1	Neutrophil count (ANC) ≥ 1.5 x 10^9/l Platelet count ≥ 100 X 10^9/l Bilirubin ≤ 1.5x ULN AST/ALT ≤3x ULN	Treatment should be deferred, and bloods repeated at least weekly, until recovery has occurred. Guidance on recommencing treatment and appropriate dose reductions are given in Section 11.5 and Table 4
8 & 15	Neutrophil count (ANC) ≥ 1.0 x 10^9/l Platelet count ≥ 75 X 10^9/l	Treatment should be omitted. Repeat bloods at least weekly until recovery. Guidance on recommencing treatment and appropriate dose reductions are given in Section 11.5 and Table 4

Table 2: Required blood parameters for paclitaxel infusion

Dose banding using the NHS England dose-banding tables for paclitaxel (https://www.england.nhs.uk/wp-content/uploads/2016/03/pss-cquin-schemes.pdf) is permitted where this is standard local practice. The use of other banding protocols must be notified to and approved by the Sponsor prior to trial initiation.

Dose capping is not recommended. However, sites may use dose- capping if this is their standard local practice and this is notified to and approved by the Sponsor prior to trial initiation.

Prior to administration of paclitaxel, hypersensitivity prophylaxis, including H1/H2 antagonists and corticosteroids, should be given as per local standards, for example, 30 minutes prior to paclitaxel one of the following may be administered:

- Dexamethasone 7.6-8 mg IV (If patients are unable to tolerate weekly dexamethasone at this dose and have not experienced paclitaxel hypersensitivity, the dose can be gradually reduced at the investigator's discretion. If a hypersensitivity reaction develops, dexamethasone should be reintroduced at least 7.6-8 mg IV prior to ALL subsequent paclitaxel infusions.)
- Chlorphenamine 10 mg IV as per local practice
- Ranitidine 50 mg IV (in 20 ml Normal Saline over 2 minutes)

- Immediately pre-chemotherapy give antiemetics as per local standards.
- Anaphylaxis precautions should be available during infusion for the emergency treatment of hypersensitivity reactions.
- Give paclitaxel intravenously over one hour via a rate-controlling device.
- Monitor closely for allergic reactions and cardiac arrhythmias as per local guidelines.
- Use of a cold cap is permitted.
- On extravasation, paclitaxel is a vesicant. Local guidelines for the management of extravasation should be followed.

11.4.2 Nab-paclitaxel

- Nab-paclitaxel will be administered at a dose of 100mg/m^2 on days 1, 8 and 15 of a 21-day cycle for a maximum of 6 cycles.
- As with paclitaxel, dose banding using the NHS England dose-banding tables is permitted where this is standard local practice. The use of other banding protocols must be notified to and approved by the Sponsor prior to trial initiation.
- Additional medication for nausea can be given to take orally after administration as required, for example, metoclopramide 10mg three times a day as required.
- If any hypersensitivity reaction occurs, stop nab-paclitaxel immediately.

11.4.3 Cediranib

Maintenance cediranib will start up to 9 weeks after cycle 1 day 1 of weekly paclitaxel. Cediranib can be initiated when bowel symptoms have abated to grade 1 or less or the risk to the patient's bowel has been minimised. Participants will be given one bottle containing 35 tablets. Further cediranib may be dispensed mid-cycle if necessary, to manage dose reductions. Within each bottle all tablets will be the same strength (either 20 mg or 15 mg).

When cediranib is introduced in combination with paclitaxel/nab-paclitaxel cycles should be documented as **day 1 being from the date of administration of paclitaxel**. If treatment cannot be given on day 1 of a cycle, it should be deferred. If treatment cannot be given on days 8 or 15, it should be omitted.

Treatment decisions should be based on the most recent bloods – it is expected that in most cases this will be up to 2 days prior to the dispensing day, though up to 4 days is permitted where this is essential (for example after a bank holiday weekend).

The 20 mg dose of cediranib can be taken with or without a light meal or snack (e.g., two pieces of toast or a couple of biscuits), in a similar way each morning. If cediranib is dose reduced to 15 mg per day then it must be taken on an empty stomach to preserve its activity—i.e. it should be taken at least 1 hour before, and at least 2 hours after, food ingestion.

Cediranib should be swallowed whole with approximately half a pint of water and not chewed, crushed, dissolved or divided. If vomiting occurs shortly after a cediranib tablet is swallowed, the dose should only be replaced if the tablet can be seen to be intact. If a scheduled dose is missed, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken and the patient should take a single dose at the next scheduled time. The number of omitted doses will be recorded in the patient's diary and transferred to the patient's notes and the CRF. If a patient's toxicity has been managed through a dose reduction or a 5 days on/ 2 days off approach, this will also be documented in the patient's notes and CRF.

For guidance on the use of cediranib in patients with reduced renal and liver function or hepatic dysfunction see section 11.10.2.2 and 11.10.2.3 of the protocol.

11.4.4 Olaparib

Patients who develop PD during paclitaxel cediranib treatment or during cediranib monotherapy will have the option to switch to cediranib and olaparib treatment, provided they continue to meet the eligibility criteria for the trial (see sections 8.3 and 8.4).

The olaparib trial treatment will be dispensed to patients for a dose of 300 mg twice daily equivalent to a total daily dose of 600 mg which is equivalent to the 400 mg capsules twice daily dose[16]. The 100 mg and 150 mg tablets will be used to manage dose reductions. On the first day of each 21-day cycle, participants will be given three bottles each containing 32 tablets. Further olaparib may be dispensed

mid-cycle if necessary, to manage dose reductions. Within each bottle all tablets will be the same strength (either 100 mg or 150 mg). Once a bottle has been opened it cannot be used after 3 months. Treatment decisions should be taken as recently as possible – it is expected that is most cases this will be up to 2 days prior to the dispensing day, though up to 4 days is permitted where this is essential (for example after a bank holiday weekend).

In this trial, olaparib is being given in combination with cediranib and this influences the way olaparib should be taken. The daily dose of cediranib and the morning dose of olaparib can be taken together and should be taken at a similar time each day; the evening dose of olaparib should be taken 12 hours after the morning olaparib dose. Treatment with olaparib and cediranib will continue as a three-weekly cycle of continuous treatment until further PD.

- If cediranib is being taken at a dose of 20 mg per day (or if cediranib is being withheld) then the morning doses of olaparib and cediranib can be taken with or without a light meal or snack (e.g., two pieces of toast or a couple of biscuits).
- If cediranib has been dose reduced to 15 mg per day then the morning doses of olaparib and cediranib must be taken on an empty stomach—i.e. at least 1 hour before, and at least 2 hours after, food ingestion.
- The evening dose of olaparib can be taken without food, or with a light meal or snack (e.g., two pieces of toast or a couple of biscuits), irrespective of the cediranib dose.
- Olaparib should be taken with half a pint of water, should be swallowed whole and not chewed, crushed or divided.
- If vomiting occurs shortly after the tablets are swallowed, the dose should only be replaced if all the intact tablets can be seen and counted.

Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., because of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time. The number of omitted doses will be recorded in the participant's diary and transferred to the participant's notes and the CRF. If a participant's toxicity has been managed through a dose reduction this will also be documented in the participant's notes and CRF. For guidance on dose reductions for cediranib and olaparib, see section 11.5.4 and 11.5.5 of the protocol.

11.5 Dose modification for toxicity

11.5.1 Paclitaxel Modification

The dose levels for Paclitaxel are as follows;

1) Starting dose: 70mg/m^2
2) Dose Level 1: 55mg/m^2
3) Dose Level 2: 40mg/m^2
4) Dose Level 3: STOP

11.5.1.1 Management of paclitaxel-related toxicities

Recommendations for the management of key paclitaxel-related toxicities are listed in table 3. The appropriate dose reductions are described in section 11.5.1 and investigators should refer to table 4 when making decisions about treatment modifications for toxicity.

There are no paclitaxel dose reductions planned for nausea, vomiting, diarrhoea, constipation or venous thrombo-embolism. These should be managed with standard appropriate supportive measures per local guidelines.

For any other AE, of CTCAE grade 4, considered at least possibly related to weekly paclitaxel, treatment should be discontinued after discussion with the TM at CTR who will liaise with the Chief Investigator (CI) and a decision will be made on the best appropriate course of action.

Event	Toxicity	Recommended action
Neutropenia	<1.5x10^9/l on D1	Defer treatment until recovered to ≥ 1.5x 10^9/l. If recovery occurs in ≤ 1 week then continue at current dose. If > 1 week then either use prophylactic Granulocyte-Colony Stimulating Factor (G-CSF) or reduce to next available dose level.

	<1.0x10^9/l on D8 or D15	Omit current dose. At next scheduled dose either use prophylactic G-CSF or reduce to next available dose level.
Febrile neutropenia	ANC<1.0 x10^9/l and temperature >38 °C	Defer treatment until recovery and then either use prophylactic G-CSF or reduce to next available dose level.
Platelets	<100x10^9/l on D1	Defer treatment until recovered to ≥ 100x 10^9/l. If recovery occurs in ≤ 1 week then continue at current dose. If > 1 week then reduce to next available dose level.
	<75x10^9/l on D8 or D15	Omit current dose. At next scheduled dose reduce to next available dose level.
	<25x10^9/l or bleeding associated with <50x10^9/	Defer treatment until platelet recovery and reduce to next available dose level.
Liver function tests	Bilirubin> 1.5xULN or AST/ALT >2.5xULN (or >5xULN in the presence of liver metastases) on D1	Defer treatment until recovery and evaluate for alternative cause. If recovery occurs in ≤ 1 week or alternative cause demonstrated continue at current dose. If recovery >1 week then reduce to next available dose level.
Neuropathy (sensory or motor)	G2	Defer/ omit paclitaxel until recovery to ≤ G1 and then reduce to next available dose level. If recovery takes >4 weeks stop paclitaxel.
	≥G3	Stop paclitaxel.
Mucositis	≥G3	Defer/ omit paclitaxel until recovery to ≤ G1 and then reduce to next available dose level.
Rash	≥ G2 (commonly affecting dorsal surface of hands/ forearms)	Supportive management such as emollients, analgesia and antihistamines at investigators discretion. Omit until recovery to ≤ G1 and then reduce to next available dose level.

Pneumonitis or PCP pneumonia	Any grade	**Discontinue paclitaxel.**

Table 3: Paclitaxel dose modification table

For more details about clinically notable adverse events, refer to the latest SmPC.

To determine the expectedness of an adverse event, refer to the current Reference Safety Information (RSI).

11.5.1.2 Management of paclitaxel-related toxicities hypersensitivity reactions

Acute management of any hypersensitivity reactions will follow local standard of care. Re-challenge with paclitaxel at full dose following a CTCAE grade 1-2 hypersensitivity reaction is permitted, if the site investigator feels that this is in the participant's best interests. Local standard of care should be followed, and consideration given to increased prophylactic medications and slowing of initial infusion rates.

Re-challenge following a CTCAE grade 3-4 hypersensitivity reaction is not recommended.

11.5.2 Table 4: Reported Nab-paclitaxel toxicities

The following toxicities are listed in the Summary of Product Characteristics for nab-paclitaxel monotherapy used at any dose. (MA Number EU/1/07/428/001. Last updated October 2020).

Body System (CTCAE v4.0)	**Toxicity**
Infections and infestations	*Common: Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis* *Uncommon: Sepsis, neutropenic sepsis, pneumonia, oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, herpes zoster, fungal infection, catheter related infection, injection site infection*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*Uncommon:* Metastatic pain, tumour necrosis.

Blood and lymphatic system disorders	*Very common*: Neutropenia, anaemia, leukopenia. thrombocytopenia, lymphopenia, bone marrow suppression. *Common*: Febrile neutropenia. *Rare*: Pancytopenia.
Immune system disorders	*Uncommon*[1]*:* Hypersensitivity. *Rare:* Severe hypersensitivity.
Metabolism and nutrition disorders	*Very common:* Anorexia. *Common:* Dehydration, decreased appetite, hypokalaemia. *Uncommon:* Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia.
Psychiatric disorders	*Common*: Insomnia, depression, anxiety. *Uncommon*: Restlessness.
Nervous system disorders	*Very common*: Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia. *Common*: Peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence. *Uncommon*: Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor.
Eye disorders	*Common:* Increased lacrimation, blurred vision, dry eye, keratoconjunctivitis sicca, madarosis.

	Uncommon: Eye irritation, eye pain, abnormal vision, reduced visual acuity, conjunctivitis, visual disturbance, eye pruritus, keratitis. *Rare*: Cystoid macular oedema.
Ear and labyrinth disorders	*Common*: Vertigo. *Uncommon*: Ear pain, tinnitus.
Cardiac disorders	*Common*: Tachycardia, arrhythmia, supraventricular tachycardia. *Rare:* bradycardia, cardiac arrest, left ventricular dysfunction, congestive heart failure, atrioventricular block.
Vascular disorders	*Common*: Flushing, hot flushes, hypertension, lymphoedema. *Uncommon*: Hypotension, peripheral coldness, orthostatic hypotension. *Rare:* Thrombosis.
Respiratory, thoracic and mediastinal disorders	*Common*: Interstitial pneumonitis, dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea. *Uncommon*: Productive cough, exertional dyspnoea, sinus congestion, decreased breath sounds, pleural effusion, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing, pulmonary emboli, pulmonary thromboembolism.
Gastrointestinal disorders	*Very common*: Nausea, diarrhoea, vomiting, constipation, stomatitis. *Common*: Abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoaesthesia.

	Uncommon: Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal haemorrhage.
Hepatobiliary disorders	*Uncommon*: Hepatomegaly.
Skin and subcutaneous tissue disorders	*Very common*: Alopecia, rash. *Common*: Nail disorder, pruritus, dry skin, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes. *Uncommon*: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, papular rash, skin lesion, swollen face. *Very rare:* Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	*Very common*: Arthralgia, myalgia. *Common*: Pain in extremity, bone pain, back pain, muscle cramps, limb pain. *Uncommon*: Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness.
Renal and urinary disorders	*Uncommon*: Dysuria, pollakiuria, haematuria, nocturia, polyuria, urinary incontinence.
Reproductive system and breast disorders	*Uncommon*: Breast pain.

General disorders and administration site conditions	*Very common*: Fatigue, asthenia, pyrexia. *Common*: Peripheral oedema, mucosal inflammation, pain, rigors, oedema, weakness, decreased performance status, chest pain, influenza-like illness, malaise, lethargy, hyperpyrexia. *Uncommon*: Chest discomfort, abnormal gait, swelling, injection site reaction. *Rare:* Extravasation.
Investigations	*Common*: Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased haematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase. *Uncommon*: Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium, increased bilirubin.
Injury, poisoning and procedural complications	*Uncommon:* Contusion *Rare:* Radiation recall phenomenon, radiation pneumonitis

Table 4 Reported Nab-paclitaxel toxicities

11.5.3 Management of nab-paclitaxel related toxicities

General toxicities should be managed with appropriate supportive measures as per local guidelines. Recommendations for the key toxicities along with dose reduction recommendations can be found in section 11.5.3 in table 5. As with paclitaxel, for AEs of CTCAE grade 4 thought to be related to nab-paclitaxel, treatment should be discontinued after discussion with the TM at CTR who will liaise with the Chief Investigator (CI) and a decision will be made on the best appropriate course of action.

11.5.4 Nab-paclitaxel dose reduction levels

The dose levels for nab-paclitaxel are as follows:

1) Starting dose: 100 mg/m^2
2) Dose Level 1: 75 mg/m^2
3) Dose Level 2: 50 mg/m^2
4) Dose Level 3: STOP

11.5.5 Table 5: Nab-paclitaxel dose modifications table

Event	Toxicity	Recommended action
Neutropenia	<1.5x10^9/l on D1	Defer treatment until recovered to ≥ 1.5x 10^9/l. If recovery occurs in ≤ 1 week then continue at current dose. If > 1 week then either use prophylactic Granulocyte-Colony Stimulating Factor (G-CSF) or reduce to next available dose level.
	<1.0x10^9/l on D8 or D15	Omit current dose. At next scheduled dose either use prophylactic G-CSF or reduce to next available dose level.
	Febrile neutropenia ANC<1.0 x10^9/l and temperature >38 °C	Defer treatment until recovery and then either use prophylactic G-CSF or reduce to next available dose level.
Platelets	<100x10^9/l on D1	Defer treatment until recovered to ≥ 100x 10^9/l. If recovery occurs in ≤ 1 week then continue at current dose. If > 1 week then reduce to next available dose level.
	<75x10^9/l on D8 or D15	Omit current dose. At next scheduled dose reduce to next available dose level.
	<25x10^9/l or bleeding associated with <50x10^9/l	Defer treatment until platelet recovery and reduce to next available dose level.
Liver function tests	Bilirubin> 1.5xULN or	Defer treatment until recovery and evaluate for alternative cause. If recovery occurs in ≤ 1 week or alternative cause demonstrated continue at current

	AST/ALT >3xULN (or >5xULN in the presence of liver metastases) on D1	dose, if recovery >1 week then reduce to next available dose level.
Neuropathy (sensory or motor)	G2 ≥G3	Defer/ omit until recovery to ≤ G1 and then reduce to next available dose level. If recovery takes >4 weeks stop nab-paclitaxel. Stop nab-paclitaxel.
Mucositis	≥G3	Defer/ omit until recovery to ≤ G1 and then reduce to next available dose level.
Rash	≥ G2 (commonly affecting dorsal surface of hands/ forearms)	Supportive management such as emollients, analgesia and antihistamines at investigators discretion. Omit until recovery to ≤ G1 and then reduce to next available dose level.
Pneumonitis or PCP pneumonia	Any grade	**Discontinue nab-paclitaxel.**

11.5.6 Cediranib Dose Modifications

A single dose reduction to 15 mg OD and the use of a 5 days on/ 2 days off dosing schedule can manage treatment-related toxicity. The 5 days on/ 2 days off dosing schedule allows the investigator flexibility in managing cediranib related toxicities but is not considered a dose reduction. The 5 days on/ 2 days off schedule can be implemented with any cediranib dose. The 7 days on schedule can be reinstated if the investigator believes this to be in the best interest of the participant and repeated 5 days on/ 2 days off schedules are allowed.

Note that if cediranib is dose reduced to 15 mg per day then it must be taken on an empty stomach to preserve its activity (see section 11.4.3).

The dosing levels for cediranib are as follows:

- Starting dose: 20 mg OD
- Dose Level 1: 15 mg OD

- Dose Level 2: STOP

Cediranib will be administered with paclitaxel, on its own as a monotherapy or with olaparib

11.5.7 Management of cediranib-related toxicities

Cediranib will be administered with paclitaxel (component 1) or olaparib (component 2). The toxicities associated with VEGF pathway inhibitors such as cediranib are well known and there are established management protocols to address these toxicities. The most common side effects observed in patients treated with cediranib include hypertension, diarrhoea, nausea, fatigue and proteinuria. Thrombo-embolism, fistula formation, bowel perforation and reversible posterior leuko-encephalopathy (RPLE) have also been associated with cediranib use.

Any patient who experiences one of the complications listed below should permanently discontinue cediranib;

1) Any grade of fistula.
2) Bowel perforation.
3) CTCAE grade 4 diarrhoea.
4) Severe persistent hypertension despite maximal anti-hypertensive treatment.
5) RPLE.
6) Arterial thrombo-embolism (e.g. myocardial infarction or cerebrovascular accident).
7) Grade 4 venous thrombo-embolism.
8) Severe haemorrhage.

The recommended management of specific toxicities is are follows:

11.5.8 Hypertension

The goal of managing cediranib-associated hypertension is to maintain BP below 150/90 mmHg. Because of hospital-related exacerbations of hypertension (white-coat phenomenon), participants should be encouraged to acquire a portable BP monitor and take regular home readings. Home readings of BP will be taken into consideration when making decisions on initiating anti- hypertensive therapy.

If serial measurements identify BP readings that exceed the threshold of 150/90 mmHg, participants will be commenced on anti-hypertensive therapy with one or more of a calcium channel antagonist

(e.g. amlodipine), an ACE inhibitor (e.g. enalapril) or another anti-hypertensive drug. If a patient is already taking anti-hypertensives, the dose of these should be increased or an additional drug added. Management of hypertension will be per local practice and the exact choice of anti-hypertensive agents will be influenced by co-morbid conditions and the toxicities of anti-hypertensive agents.

Patients who develop CTCAE grade 4 hypertension (life-threatening consequences e.g. hypertensive crisis, transient or permanent neurologic deficit) or RPLE should permanently discontinue cediranib.

11.5.9 **Proteinuria**

Proteinuria is a common but usually clinically non-significant toxicity. Proteinuria will be monitored by dipstick examination of urine every 4 weeks in clinic. If the urine contains at least 3+ protein, a sample will be sent to test for infection and a 24-hour collection will be made to quantify the protein output. If urinary protein excretion is more than 2 g/24 hours, cediranib will be held until the toxicity has resolved to CTCAE grade I or less (<1 g/ 24 hours) and then recommenced at the next available dose level (section 11.5.2). It is recommended that 24-hour urinary protein excretion is repeated weekly until resolution

11.5.10 **Thromo-embolic events**

The prevalence of venous thrombo-embolism is slightly increased in patients receiving VEGF inhibitors. For patients who develop thrombosis/embolism during cediranib treatment, the following action is recommended:

- Cediranib should be permanently discontinued in patients who develop any grade of arterial thromboembolic event e.g. Myocardial infarction or ischaemic cerebrovascular event.
- CTCAE grade 2 Venous thromboembolic event; commence therapeutic dose anti-coagulant therapy with low molecular weight heparin. Cediranib can be continued or withheld for up to 2 weeks at clinician's discretion.
- CTCAE grade 3 or incidentally discovered pulmonary embolus; hold cediranib for up to 2 weeks. Commence therapeutic-dose low molecular weight heparin, Recommence cediranib when stable.
- Symptomatic CTCAE grade 4 venous thromboembolic events; permanently discontinue cediranib.

11.5.11 **Diarrhoea**

Diarrhoea has been commonly reported in patients receiving cediranib. 11% of patients receiving 20mg OD in the maintenance phase of ICON6 trial suffered G3 diarrhoea. It is important to adopt a clear management strategy to rapidly control symptoms associated with diarrhoea.

All participants receiving cediranib in CEBOC should be counselled that they are likely to experience diarrhoea during treatment and prescribed loperamide to use in case diarrhoea occurs. If diarrhoea develops, they should immediately commence loperamide and inform the local trial PI or research nurse. Guidance on management dependent on severity of diarrhoea is given in table 5.

CTCAE (current) severity	**Recommended action**
Grade 1 (Increase of <4 stools per day from baseline)	Commence loperamide as recommended. Follow dietary advice and ensure adequate fluid intake. Continue cediranib dosing.
Grade 2 (increase 4-6 stools per day or nocturnal diarrhoea)	Commence loperamide. Follow dietary advice and ensure adequate fluid intake. If not reduced to ≤ G1 within 24 hours, hold cediranib for at least 48 hours. Resume dosing when ≤ G1 at same dose. If G2 diarrhoea recurs, reduce cediranib dose to next dose level at recovery or consider 5 days on, 2 days off dosing at current dose.
Grade 3 (increase of ≥ 7 stools per day or requiring intravenous rehydration or hospitalisation)	Commence loperamide, intravenous hydration as required. Hold cediranib for at least 48 hours and until recovery to ≤G1. On recovery reduce cediranib to next dose level or consider 5 days on, 2 days off dosing at current dose
Grade 4 (life-threatening consequences)	Commence loperamide. Resuscitate. **Permanently discontinue cediranib.**

Table 6: Management of cediranib-associated diarrhoea

For more details about clinically notable adverse events, refer to the latest Investigator Brochure (IB). To determine the expectedness of an adverse event, refer to the current Reference Safety Information (RSI).

The recommended loperamide regimen is 4mg at the first episode of loose stool and then 2mg every 2-4 hours until participant is free from diarrhoea for at least 12 hours. Alternative regimens consistent with established local practice may be used.

Participants should be advised to modify their diet during episodes of diarrhoea as an adjunct to loperamide treatment. Current best recommendations are to; eat low-fat, high protein food and stay away from fatty, high-fibre or spicy foods. Eat cooked vegetables instead of raw vegetables. Take off the skin of fruits before eating them. Stay away from milk, milk products and herbal supplements. Eat 2 grated apples a day that have been left after grating for at least 1 hour to oxidise (skin peeled off).

11.5.12 **Fatigue**

Mild to moderate fatigue is commonly seen with cediranib therapy and can be rapid in onset. CTCAE grade 3 fatigue was seen in 16% participants when cediranib was given in combination with chemotherapy and 6% patients during cediranib maintenance therapy in the ICON6 trial. Fatigue can often be managed successfully with short treatment breaks without reducing cediranib dose and participants should be advised to seek advice from the research team early in the event of ≥ CTCAE grade 2 fatigue (not relieved by rest and interfering with normal levels of activity).

The research team should evaluate for other causes of fatigue, especially other cediranib-related toxicities such as diarrhoea and hypothyroidism. Advice on cediranib dosing in the event of fatigue is given in Table 7.

CTCAE (current version) severity	**Recommended action**
Grade 1 (relieved by rest)	Continue cediranib dosing.
Grade 2 (not relieved by rest, affecting instrumental ADLs)	Hold cediranib dosing for at least 48 hours and until improved to ≤G1. Check TFTs. If recovery within 1-week restart at current dose level. If recovery longer than 1 week consider 5 days on, 2 days off dosing at current dose or reduce to next dose level.
Grade 3 (not relieved by rest, affecting self-care ADLs)	Hold cediranib dosing for at least 48 hours and until improved to ≤G1. Check TFTs. At recovery, restart cediranib but use 5 days on, 2 days off dosing at current dose or reduce to next dose level.

Table 7: Management of cediranib-associated fatigue

For more details about clinically notable adverse events, refer to the latest Investigator Brochure (IB). To determine the expectedness of an adverse event, refer to the current Reference Safety Information (RSI).

11.5.13 **Abnormal Thyroid Function Tests**

Cediranib treatment can cause hypothyroidism and up to 25% of patients receiving develop abnormal TFTs during cediranib therapy. In most cases, these are asymptomatic and do not require intervention. TFTs should be checked in all patients with ≥G2 fatigue and thyroid replacement therapy initiated for symptomatic hypothyroidism as per standard local practice. Cediranib dosing should not be altered for hypothyroidism although treatment may be held until resolution of symptoms at the discretion of the local investigator.

11.5.14 Other cediranib-related toxicities

Other expected AEs for cediranib include nausea/ vomiting, dysphonia (hoarseness), oral mucositis and thrombocytopenia. These are generally mild and overlap with the expected toxicities for olaparib and paclitaxel. Investigators should follow specific guidance for olaparib and paclitaxel dosing. If in the investigator's opinion, cediranib has made a significant contribution to an AE, then general guidance for cediranib dosing is given in table 8.

Guidance can be sought from the CIs via the CTR TM if required.

CTCAE (current version) severity	**Recommended action**
Grade 1	Symptomatic care. Continue cediranib dosing
Grade 2	Symptomatic care. Hold cediranib dosing if toxicity does not recover to ≤G1 within 48 hours. On recovery resume dosing at current dose level. If toxicity recurs, consider 5 days on, 2 days off dosing at current dose or reduce to next dose level.
Grade 3	Symptomatic care. Hold cediranib dosing if toxicity does not recover to ≤G1 within 48 hours. On recovery, restart cediranib but use 5 days on, 2 days off dosing at current dose or reduce to next dose level.
Grade 4	**Permanently discontinue cediranib**

Table 8: Management of cediranib-associated other related toxicities

For more details about clinically notable adverse events, refer to the latest Investigator Brochure (IB).

To determine the expectedness of an adverse event, refer to the current Reference Safety Information (RSI).

11.5.15 Olaparib dose reduction levels

Olaparib will be administered concurrently with cediranib in patients if they remain eligible to participate after they develop PD on the first component of the trial. As these drugs have a partially overlapping toxicity spectrum, investigators should evaluate carefully which drug is the likely cause of AEs on treatment and refer to the guidance in this section when deciding management strategy.

The dosing levels for olaparib are as follows;

1. Starting dose: 300 mg BD
2. Dose Level 1: 250 mg BD
3. Dose Level 2: 200 mg BD
4. Dose Level 3: STOP

11.5.16 Management of olaparib-related toxicities

The most frequently observed adverse reactions (ARs) across clinical trials in patients receiving olaparib monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, anaemia, neutropenia, lymphopenia, cough, mean corpuscular volume elevation and increase in creatinine. For the most part these are CTCAE grade 1 or 2 and do not require treatment discontinuation. In general, olaparib should be discontinued if the following AESI's occur:

- Bone marrow findings consistent with MDS/acute myeloid leukaemia AML.
- Severe persistent anaemia.
- Pneumonitis.

11.5.17 Haematological toxicities

Anaemia and other haematological toxicities are generally low grade (CTCAE grade 1 or 2). Pre-treatment testing followed by monthly monitoring of complete blood counts is mandatory during the trial and clinically significant changes during treatment in any parameter should be managed as per

protocol guidance. Common treatable causes of anaemia should be excluded in all cases of anaemia including iron, Vitamin B12 and folate deficiencies and hypothyroidism.

In the event of CTCAE grade 3 or grade 4 haematological toxicity, complete blood counts should be checked at least weekly until recovery to grade 1 or better. Table 9 below shows that guidelines for managing haematological toxicities in participants taking olaparib

Event	Toxicity	Recommended action
Anaemia	Grade 2: 80 < Hb ≤ 90 g/l	PI to investigate and manage as they deem appropriate. Treatment options include interruption of olaparib for up to 4 weeks, or olaparib dose reduction, considering previous history of anaemia. After 4 weeks, if Hb remains low (80 < Hb ≤ 90 g/l), dose interrupt (up to total interruption of 4 weeks) until Hb ≥ 90 g/l. Upon recovery (Hb > 90 g/l) consider reducing olaparib to next available dose level. Cediranib can be continued at the PI's discretion.
	Grade 3 or worse: Hb < 80 g/l	Interrupt olaparib treatment for up to 4 weeks* until Hb ≥ 90 g/l. Give supportive management including transfusion* and initiate appropriate haematological testing. Upon recovery to Hb ≥ 90 g/l, olaparib should be restarted at the next available dose level. If Hb decreases again, immediately reduce to next available dose level. Cediranib can be continued at the PI's discretion.
Neutropenia	Grade 3 or 4 (ANC <1.0 x10^9/l)	First occurrence: interrupt olaparib treatment for up to 4 weeks* until recovered to CTCAE grade 1 or better (ANC ≥ 1.5 x 10^9/l).

Febrile neutropenia	Grade 3 or worse (ANC <1.0 x10^9/l and temperature > 38°C)	Repeat occurrence: interrupt olaparib treatment for up to 4 weeks until recovered to CTCAE grade 1 or better (ANC ≥ 1.5 x 10^9/l). Recommence olaparib at the next available dose level. Cediranib can be continued at the PI's discretion. Primary prophylaxis with G-CSF is not recommended. Interrupt olaparib treatment until neutrophil recovery to CTCAE grade 1 or better (ANC ≥ 1.5 x 10^9/l), then dose reduce and recommence olaparib at the next available dose level. Prophylaxis with G-CSF can be used in accordance with local guidelines. G-CSF should not be used within 24 hours of the last dose of olaparib. Growth factor support should be stopped at least 24 hours before restarting olaparib (7 days for pegylated G-CSF). Cediranib can be continued at the PI's discretion.
Thrombocytopenia	Grade 3 or worse (platelets < 50 x 10^9/l)	Interrupt treatment with both olaparib and cediranib for up to 4 weeks* until recovery to CTCAE grade 1 or better (platelets > 75 x 10^9/l). If recovery (platelets > 75 x 10^9/l) occurs within 2 weeks, and thrombocytopenia was not worse than grade 3 (platelets > 25 x 10^9/l), resume cediranib and olaparib dosing at current levels. If CTCAE grade 4 thrombocytopenia (platelets < 25 x 10^9/l) had occurred, or recovery takes longer than 2 weeks, then once recovered, recommence olaparib at the next available dose level. Cediranib dosing can be resumed at the same level.

* If a participant has a ≥2-week interruption in olaparib due to CTCAE grade 3 or worse anaemia, neutropenia (CTCAE lists as decrease in neutrophil count) or thrombocytopenia (CTCAE lists as decrease in platelet count), or if they develop blood/platelet dependence then refer to the information below on prolonged haematological toxicities.

Table 9: Management of olaparib-associated haematological toxicities

If a patient develops prolonged haematological toxicity such as:

- ≥2-week interruption/delay in olaparib treatment due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence.
- ≥2-week interruption/delay in olaparib treatment due to CTCAE grade 3 or worse neutropenia (ANC < 1 x 10^9/L).
- ≥2-week interruption/delay in olaparib treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L).

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage per standard haematological practice. Olaparib treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator.

11.5.18 Management of non-haematological toxicities

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is >4 weeks, the TM must be informed. Where toxicity recurs following re-challenge with study treatment, 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 study treatment.

Olaparib treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any CTCAE grade 3 or 4 AE occurs which the investigator considers to be related to administration of study treatment.

11.5.19 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further 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 study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the CI via the TM. If olaparib causes pneumonitis, olaparib should be discontinued.

11.5.20 Management of Gastrointestinal (GI) toxicities

Gastrointestinal toxicities are frequently reported with olaparib therapy and are generally low grade (CTCAE grade 1 or 2) and intermittent and can be managed by dose interruption and/or concomitant medicinal products (e.g. single agent antiemetic therapy). Routine antiemetic prophylaxis is not required but appropriate therapy should be provided at the first onset of nausea or vomiting and as required thereafter, per local treatment practice guidelines.

In the event of diarrhoea, please refer to the cediranib management guidelines (section 11.5.1.1 and table 4).

In the event of repeated frequent episodes of grade 2 gastro-intestinal toxicity, related to olaparib, a dose reduction to the next available level should be considered.

In the event of grade 3 gastrointestinal toxicity, considered related to olaparib and not resolving to ≤ CTCAE grade 1 within 48 hours with supportive care, olaparib dosing should be held and subsequently restarted at a reduced dose.

11.5.21 Management of abnormal renal function during olaparaib therapy

A dose reduction is recommended for participants who develop moderate renal impairment (creatinine clearance of between 31 and 51 ml/min) for any reason during the study: the dose of olaparib should be reduced to 150 mg BD.

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 that olaparib be discontinued.

11.5.22 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events 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 for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic antiemetic treatment is required at the start of study treatment; however, patients should receive appropriate antiemetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of biscuits).

As per international guidance on antiemetic use in cancer patients (The European Society for Medical Oncology, National Comprehensive Cancer Network), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines or dexamethasone.

11.5.23 Management of other toxcities considered to olaparib

A flexible approach will be taken to allow participants to gain maximum benefit from treatment. Any toxicity observed during the trial that is deemed related to olaparib can be managed by olaparib treatment interruption if deemed appropriate by the investigator. Repeat dose interruptions for grade 2 toxicity are allowed as required, for a maximum of 4 weeks on each occasion. Trial treatment must

be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) CTCAE (current version) grade 1 or less. See table 10 for further guidance.

CTCAE (current version) Severity	**Recommended action**
Grade 1	Symptomatic care. Continue olaparib dosing.
Grade 2	Symptomatic care. Hold olaparib dosing if toxicity does not recover to ≤G1 within 48 hours. On recovery resume dosing at current dose level. If toxicity recurs, continue current dose or reduce to next dose level at investigator's discretion.
Grade 3	Symptomatic care. Hold olaparib dosing if toxicity does not recover to ≤G1 within 48 hours. On recovery, restart olaparib but reduce to next dose level.
Grade 4	**Discontinue olaparib**

Table 10: Management of olaparib-associated other related toxicities

11.5.24 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolutions, should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to PD or toxicity, the case should be discussed with the CI via the TM.

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

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks providing any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur. Please refer to table 9 for further guidance recommended management of specific olaparib toxicities.

11.6 Continuations of cediranib or olaparib as monotherapy due to toxicity

In the vast majority of circumstances cediranib and olaparib should be discontinued at the same time however, in rare circumstances, participants experiencing ongoing clinical benefit, who develop a toxicity related to either cediranib or olaparib that prevents them from taking further doses of one of the IMPs, may be permitted to continue taking the other IMP, if the risk benefit remains favourable and after discussion with the CI via the CTR.

11.7 Management of overdose

The trial 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 must be reported as an overdose.

In the event of an overdose, the physician will administer the most appropriate treatment for the participant and treat any ARs associated with the overdose symptomatically.

Overdoses must be initially reported to the CTR within 24 hours of the research team becoming aware of the overdose. To report an overdose, the research team must complete a protocol dosing error form and email or fax a copy to the CTR Safety Team ctr-safety@cardiff.ac.uk and cc CEBOC@cardiff.ac.uk. The local research team is responsible for the completion of this form and the PI is required to sign the form. The local research team is required to provide the CTR with any requested follow-up information as soon as possible.

An overdose is not an AE and may not result in any noticeable effect on the participant. However, if the participant experiences a SAE that the PI considers may be causally related to an overdose, then this must be clearly stated on the SAE form Any resulting SAE will be reported following standard reporting procedures for SAEs (see section 13 for SAE reporting procedures).

11.7.1 Overdose of cediranib

There is no specific treatment for cediranib overdose. In cases of suspected overdose, cediranib should be discontinued until ARs have resolved, BP monitored, and appropriate supportive care instituted. If the PI wishes to recommence cediranib treatment they must first obtain written permission from the CI (via the CTR).

11.7.2 Overdose of olaparib

There is currently no specific treatment for overdose of olaparib and possible symptoms are not established. In the event of an overdose with olaparib, the drug should be stopped until ARs have resolved and appropriate supportive care should be instituted. If the PI wishes to recommence olaparib treatment they must first obtain written permission from the CI (via the CTR).

11.8 Prohibited medications and interaction with other drugs

11.8.1 Cediranib – Potent UCT/Pgp Inducers

Use of cediranib should be avoided with the following potent inducers of UCT/PgP (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's Wort). Cediranib is not an inhibitor of Multi-Drug Resistance Gene-1 (MDR-1), but it has a low potential to inhibit Breast Cancer Resistance Protein (BCRP). The possibility that cediranib may induce GI CYP3A and UDP-glucuronosyltransferase (UGT) enzymes cannot be excluded.

11.8.2 Olaparib – related interactions

Olaparib can inhibit CYP3A4 and uridine di-phosphoglucuronosyl transferase 1A1 (UGT1A1) enzyme in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods such as grapefruit juice and drugs known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 28 days after the last dose of trial medication.

Co-administration of CYP3A4/Pgp inhibitor with cediranib does not require a prior dose adjustment although potent inducers of CYP3A4, UGT and Pgp can affect the exposure of cediranib through induction of a transporter mechanism such as Pgp.

Specific guidance on restricted medication with olaparib is given below:

11.8.2.1 Strong of Moderate CYP3A inihibitors

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 100mg 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.

11.8.2.2 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 (e.g. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

11.8.2.3 P-gp Inhibitors

It is possible that co-administration of P-gp inhibitors (e.g. amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

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

- CYP3A4 - 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

11.9 Permitted concomitant medications

Concomitant medication may be given if clinically mandated. Details (including doses, frequency, route and start and stop dates) of the trial IMP and the concomitant medication given must be recorded in the patient's medical records and CRFs. Recording of concomitant medication should continue until 28 days after the last dose of the trial IMPs.

11.9.1 Other drugs

Ondansetron and related drugs which impact the QTc interval should be used with caution.

11.10 Other trial restrictions

11.10.1 Special Warning and precautions/restrictions during the study for olaparib

11.10.1.1 Haematological

Patients should not start olaparib until they have recovered from the myelosuppressive effects of prior cytotoxic therapy. In a small number of patients who received olaparib, MDS and AML have been reported usually in patients with germline BRCA gene mutations and in whom there were additional haematological risk factors such as prior cytotoxic therapy or radiation treatment.

11.10.1.2 Pneumonitis

Pneumonitis has been reported in a small number of patients, without a clear underlying cause. If patients present with shortness of breath, worsening respiratory symptoms or with radiological abnormalities on imaging of the chest then olaparib should be stopped and prompt investigation initiated. If pneumonitis is confirmed olaparib should be stopped and appropriate treatment sought.

11.10.1.3 Grapefruit juice

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

11.10.2 Special Warning and precautions/restrictions during the study for cediranib

11.10.2.1 Elderly (>65 years)

No adjustment in starting dose is required for elderly patients. There are limited data in patients aged 75 or over.

11.10.2.2 Renal Impairment

No dose adjustment is recommended for patients with mild (creatinine clearance ≥60 mL/min to <90 mL/min) or moderate (creatinine clearance ≥30 mL/min to <60 mL/min) renal impairment, based on population PK analysis. No data are available in patients with severe (creatinine clearance <30 mL/min) renal impairment or patients on dialysis.

11.10.2.3 Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). No data are available in patients with severe Hepatic impairment.

11.10.3 General Warnings and precautions for all trial treatments

11.10.3.1 Pregnance and Teratogenicity

All IMPs should be avoided

11.10.3.2 Contraception

Female patients of childbearing potential, must agree to the use of highly effective forms of contraception for 4 weeks before entering the trial, throughout period of taking study treatment and

for 6 months after last dose of study drug. For the list of acceptable contraceptive methods see the exclusion criteria in section 9.

11.10.3.3 Surgery

If a patient requires surgery, cediranib and olaparib should be stopped at least 2 weeks prior to scheduled surgery. Cediranib and olaparib can be re-started a minimum of 2 weeks after surgery provided the patient has recovered from surgery and the wound has healed satisfactorily. If the surgery was performed for PD, the patient should stop trial treatment.

11.10.3.4 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 PD during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks provided any bone marrow toxicity has recovered.

11.10.3.5 Anti-emetics

From screening, onwards, should a patient develop nausea or vomiting, then these symptoms should be reported as AEs and appropriate treatment of the event given as per local guidelines.

11.10.3.6 Prohibited treatments

The following treatments are not allowed while the participant is on this trial treatment and or during the follow up:

- No other chemotherapy, sex-hormonal therapy or other novel agent is to be permitted during the trial for any participant.
- No other IMP can be administered while the patient is on the trial.
- Live virus and bacterial vaccines should not be administered whilst the participant is receiving trial IMP and during the 28 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.

11.11 Supportive Care

Patients participating in CEBOC are at risk of developing bowel obstruction. They will receive supportive care for paclitaxel/nab-paclitaxel in accordance with the local standards of care. However, in addition patients will have access to a symptom control team and dieticians to optimise symptoms related to bowel function or any other toxicity incurred through the protocol related treatments.

11.12 Accountability procedures

The site clinical trial pharmacist will account for the bulk supply of IMPs and all study drugs dispensed to and returned from participants, unused study drugs and for appropriate destruction. Site and patient specific IMP accountability logs will be maintained at site and IMP reconciliation will be carried out by the TM in accordance with the trial monitoring plan.

Please refer to the CEBOC Pharmacy Manual for more information about IMP management and disposal.

11.13 Compliance

The administration of all study drugs should be recorded in the CRF. Participants will self-administer olaparib/cediranib and should be given clear instructions on how and when to take their study treatment.

Participants will be monitored for treatment compliance and for attendance at protocol-scheduled visits. Participants will be instructed to record dates of missed or held doses in their patient diary and to notify study site personnel of missed doses. At each clinic visit, the participants will be asked to confirm drug doses taken or omitted and to return their bottle(s) of olaparib/cediranib. Trial site staff will count the number of tablets returned and record any missed doses in the CRF. Participant diaries will not be collected by the CTR.

12 Trial visits and procedures

The order of visits in the trial will depend on the treatment the participant is receiving and whether the participant withdraws or disease progresses.

1- Screening for eligibility (this may require multiple visits to complete all tests)
2- Registration
3- Treatment

a. Component 1: Paclitaxel/Nab-paclitaxel and Cediranib
b. Component 2: Cediranib and Olaparib

4- CT scans every 3rd cycle

5- End of treatment assessment

Telephone assessments are permitted if the participant is unable to attend the hospital site from cycle 3 of oral IMP onwards only. Urinalysis, Blood and BP assessments can be done locally (GP/local hospital) if the patient is unable to attend the site. BP assessment is important for patients on olaparib and cediranib due to cediranib AEs. Records of all assessments, reports/results and telephone consultations must be updated in the patient notes. If a patient is unable to have bloods, BP and urinalysis assessments contact CTR immediately to discuss if the patient can continue on trial treatment.

12.1 Screening for eligibility and registration

Before any study specific procedures are carried out, the subject must have signed the ICF.

Screening tests to determine participant's eligibility should be carried out within 28 days before cycle 1 day 1 of paclitaxel/nab-paclitaxel therapy. Evaluation of the subject's eligibility, date of birth and complete medical history should be undertaken during the screening phase and will include the following:

1) History of cancer, including histopathological diagnosis, grade and FIGO stage.
2) Prior cancer regimens, therapies and procedures.
3) Assessment of current symptoms, signs of cancer and treatment of symptoms.
4) Current disease status.
5) Past and concomitant non-malignant diseases.
6) All medications taken and procedures carried out within 4 weeks prior to enrolment.
7) A CT scan (taken in the 28 days before start of treatment) of the abdomen and pelvis to allow assessment of an objective response per RECIST, v1.1.
8) ECOG performance status and ECG.
9) Safety laboratory assessments including Full blood count (Hb, neutrophils, platelets), Biochemistry (Na, K, urea, Creatinine, Calcium, Phosphate, Albumin, Bilirubin, ALT or AST, ALP, GGT, LDH. TFTs CA 125, & renal function test (GFR) (refer to the schedule of assessments).

10) Urine analysis (dipstick) for proteinuria.

11) A standard examination will be carried out. Additional assessment will include:

- Height (cm), Weight (kg), Pulse rate, BP and temperature.
- Pregnancy test (where applicable).

The Physical Exam (PE) findings will be documented in the source documents and relevant parameters will be collected in the CRF.

12.2 Component 1 (Paclitaxel/Nab-paclitaxel and Cediranib)

Participants on component 1 of the protocol will start with weekly paclitaxel/nab-paclitaxel therapy. Cediranib will only be introduced when bowel symptoms have reduced to a maximum of grade 2. The combination treatment of paclitaxel/nab-paclitaxel and cediranib will start within 2-3 cycles or 6-9 weeks of treatment once all bowel symptoms have settled.

Weekly paclitaxel doses will be modified or delayed in accordance with local practice. Participants who have PD on paclitaxel/nab-paclitaxel, will be withdrawn from trial treatment. However, participants completing six three-weekly cycles of paclitaxel /nab-paclitaxel, or if paclitaxel/nab-paclitaxel has been stopped for reasons of toxicity and/or reaction to the drug will be eligible to continue single agent cediranib until further PD.

12.3 Component 2 (Cediranib and Olaparib)

Regardless of whether the participant develops PD while receiving paclitaxel/nab-paclitaxel and cediranib or during the cediranib maintenance treatment, upon progression participants will be eligible to switch treatment regimen to component 2 a combination of continuous daily oral cediranib 20 mg od with olaparib 300 mg bd.

Entry into this component of the trial requires that participants fulfil the eligibility criteria in sections 10.3 and 10.4. If eligibility is confirmed, participants will undergo assessments as detailed in section 12.4, which will be based on a 3-weekly cycle of treatment:

Treatment on component 2 will continue until second PD unless one of the following occurs:

- The patient asks to withdraw.
- The patient experiences unacceptable toxicity.

- The patient is intolerant of the treatment.

Eligible patients should also undergo assessment of germline BRCA status. This can occur during screening or while on treatment with the combination. In addition, if germline BRCA testing has been performed previously then the test does not need to be repeated.

12.4 Treatment Schedule for Component 1 and Component 2

All participants eligible for treatment for component 1 and component 2 should undergo the following assessments (refer to Table 11and 12):

1) PE (day 1 of each cycle).
2) ECOG Performance status (day 1 of each cycle).
3) AE Evaluation (day 1 of each cycle).
4) Concomitant medications (day 1 of each cycle).
5) Radiological assessment of PD by (CT scan) by RECIST v1.1 (every 3rd cycle until PD)
6) Urine analysis (dipstick) for proteinuria (day 1 of each cycle).
7) Pregnancy test (where applicable).
8) Vital signs include BP and temperature (day 1, 8 and 15 of each cycle)*.
9) Blood will be taken for full blood count (haemoglobin, neutrophils, platelets) (days 1, 8 and 15 of each cycle)*.
10) Biochemistry (Na, K, Urea, Creatinine, Calcium, Phosphate, Albumin, Bilirubin, ALTor AST, ALP, GGT, LDH) (days 1 of each cycle).
11) TFTs (day 1 of each cycle).
12) CA125 (day 1 of each cycle).

The acceptable time windows for the trial events and assessments are:

Hospital visits, D 1, 8 and 15:	+/- 2 days (blood tests ≤ 4 days prior)
CT scans:	+/- 1 week
Monthly assessments:	+/- 1 week
End-of-treatment assessment:	Min 30 days for toxicity assessment

Tables 11 and 12 refer to the following key:

a) When the participant stops the 6 cycles of paclitaxel/nab-paclitaxel and continues the maintenance cediranib therapy in component 1, the participant will only need to attend clinical on day 1 of each cycle.

b) Cediranib 20 mg od will continuously be introduced once bowel symptoms have been reduced to a maximum grade 2 until PD. Participants will have the option to stop paclitaxel/nab-paclitaxel and continue cediranib as a single agent, if participant has completed 6 cycles of paclitaxel/nab-paclitaxel or cannot continue taking paclitaxel/nab-paclitaxel due to toxicity or reaction.

c) Paclitaxel 70mg/m^2/week or nab-paclitaxel 100mg/m^2/week for six 3-weekly cycles. Weekly paclitaxel/ nab-paclitaxel doses will be modified or delayed in accordance with local practice. Beyond 6 cycles (18 weeks) or in the event of early cessation of paclitaxel/ nab-paclitaxel (e.g. because of toxicity or reaction), cediranib can be continued as a single agent.

d) Germline BRCA testing should be carried out for any participant who it is starting treatment with the combination of olaparib or cediranib. The test does not need to be performed before the start of treatment and can be perform during treatment. Also, if the participant has undergone previous germline BRCA testing, a repeat investigation is not needed.

Table 11 Schedule of assessments: Paclitaxel/nab-paclitaxel **and cediranib (Component 1)**

Observation/ Investigation	Screening	Treatment Phase Cycles 1-6 until progression*																					Every 3rd Cycle	End of treatment Follow up
		Week 1 (Days 1-7)							Week 2 (Days 8-14)[a]							Week 3 (Days 15-21)[a]								
	≤ 28 days Pre 1st dose	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Written informed consent	x																							
Demographics	x																							
Medical history	x																							
Pregnancy test (where applicable)	x	x																						x
Adverse Event Evaluation	x	x																						x
Concomitant treatments	x	x																						x
Radiological Disease treatment (CT scan)	x																						x	x
Urine Dipstick	x	x																						x
ECG	x																							x
PE	x	x																						x
Vital signs	x	x							x							x								x
FBC	x	x							x							x								x
Biochemistry	x	x																						x
GFR (using modified Wright or Cockcroft-Gault formula)	x																							
CA125 &TFTs	x	x																						x
ECOG Performance status	x	x																						x
*Cediranib(Oral)[b]		x																						
Paclitaxel/ nab-paclitaxel - infusion[c]		x							x							x								

Table 12 Schedule of assessments: Cediranib and Olaparib (Component 2)

Observation/ Investigation	Screening	Treatment Phase Cycles 1-6 until progression*																					Every 3rd Cycle	End of treatment Follow up
		Week 1 (Days 1-7)							Week 2 (Days 8-14)							Week 3 (Days 15-21)								
	≤ 28 days Pre 1st dose	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Written informed consent	x																							
Pregnancy test (where applicable)	x	x																						x
Adverse Event Evaluation	x	x																						x
Concomitant treatments	x	x																						x
Radiological Disease treatment (CT scan)	x																						x	x
Urine Dipstick	x	x																						x
ECG	x																							x
PE	x	x																						x
Vital signs	x	x																						x
FBC	x	x																						x
Biochemistry	x	x																						x
GFR (using modified Wright or Cockcroft-Gault formula)	x																							
CA125 &TFTs	x	x																						x
Germline BRCA testing [(d)]	x																							
ECOG Performance status	x	x																						x
Cediranib (Oral)		x																						
Olaparib (Oral)		x																						

12.5 Follow-up

All patients will be followed up 28 days after the last dose of study drug or for at least 18 weeks after starting cediranib. AEs that occurred while the patient was on study that are attributed to the study drug and are either still present 28 days after the last dose or occur in the 28 days post dose, will be recorded.

Patients will be followed up on protocol until PD has occurred or the patient withdraws permission. The date of death or last contact will be collected up until the point of trial closure. Sites will check the medical notes they hold for that patient. Remote follow-up will stop if the patient has died or the trial ends.

The follow-up visit will include:

- Assessment of AEs and PE.
- Radiological assessment of PD by (CT scan) by RECIST 1.1 evaluation.
- ECG.
- ECOG performance status.
- Concomitant medications.
- Urine analysis (dipstick) for proteinuria.
- Vital signs include BP and temperature.
- Blood will be taken for full blood count (haemoglobin, neutrophils, platelets), biochemistry (Na, K, Urea, Creatinine, Calcium, Phosphate, Albumin, Bilirubin, ALT or AST, ALP, GGT, LDH), CA125 and TFTs.
- Pregnancy test (where applicable).

12.6 Scanning and radiation

The protocol will result in patients receiving up to two extra CT scans of the abdomen and pelvis in excess of standard of care. While ionizing, radiation is associated with risks of second malignancy, the patient group recruited to this study have advanced recurrent, chemo-resistant ovarian cancer that is at risk of the potentially fatal complication of malignant bowel obstruction. Thus, the risks to this population are considered minimal.

13 Pharmacovigilance

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

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 16.2). This includes SAEs related to IMPs and non-Investigational Medicinal Products (nIMPs).

13.1 Definitions

Table 13

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.2 Trial Specific SAE Reporting requirements

All AEs that occur between informed consent and end of trial treatment must be recorded in the patient notes and in the appropriate section of the trial CRF. The end of trial is defined as 28 days after the last treatment visit. Details on what information is required will be detailed in the CRF and CRF completion guidelines.

In addition to the SAE reporting requirements above, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- ANY event of MDS/AML
- New primary malignancy
- Pneumonitis grade 2 or above

The listed events are adverse events of special interest (AESI), and they are events of scientific and medical interest specific to the further understanding of olaparib's safety profile, and require close monitoring and rapid communication by the investigators to AZ. An AESI may be serious or non-serious. These events should be reported to AZ Patient Safety whether it is considered a non-serious AE [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality. **All AESI must continue to be reported until the end of the trial.**

For the purposes of this trial the following events will not require reporting as SAEs:

- Bowel obstruction
- PD
- Elective hospitalisation and surgery for treatment of disease
- Elective hospitalisation to simplify treatment or study procedures
- Admissions for palliative care
- Disease related deaths

These should be completed in the participant's notes and on the relevant toxicities CRF page and forwarded to the CTR in the normal timeframes for CRFs.

13.3 Causality

Causal relationship will be assessed for IMPs, other trial treatments (nIMPs) and procedures:

IMPs: Paclitaxel, Cediranib, Olaparib and Nab-paclitaxel

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 14

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the IMP?**
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No

Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

13.4 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on the content of the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease.

SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the RSI is considered unexpected.

The table below lists the RSI's that should be referenced

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment

Paclitaxel	Sites will use paclitaxel from pharmacy stock and manufacturers include: Accord Healthcare Ltd, Hospira UK Ltd, Actavis UK Ltd, medac GmbH. Irrespective of the brand used at site, for the RSI the SmPC from Accord Healthcare Ltd for paclitaxel 6 mg/ml concentrate for solution for infusion will be used.	Section 4.8
Nab-paclitaxel	SmPC Abraxane 5 mg/ml powder for suspension for infusion	Section 4.8
Cediranib	IB Astrazeneca v23, 14 September 2020	Section 5.6
Olaparib	IB Astrazeneca Version 19, 06August2020	Section 5.6

Table 15

RSI on any CTR trial will be reviewed regularly according to CTR procedures.

13.5 Reporting procedures

13.5.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether the events had the same date of onset.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number:

0203 0432 376

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 28 days after the participant receives their last dose of the IMP. Serious adverse reactions (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow up.

Adverse events (AE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The toxicity grades should be recorded on the toxicity part of the CRF.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event / Adverse Reaction
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted, and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 16.1.

13.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 28 days after the participant receives their last dose of the investigational medicinal product. Serious adverse reactions should continue to be reported until the end of follow up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA, Main Ethics Committee and AZ.

13.6 SUSAR reporting

The University of Manchester is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (MHRA and relevant ethics committees) and to AZ as follows:

SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR. If report is then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report.

SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR. Any additional, relevant information must be reported within a further 15 days.

13.7 Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA, REC, trial sponsor and AZ in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

The CTR safety team will advise AZ by email of all SAEs within 1 business day of the unit becoming aware of the SAE. If required, the CTR will send copies of all SAE forms to AZ.

13.8 Contraception and pregnancy

Olaparib and Cediranib should not be used during pregnancy. Patients of childbearing potential on the trial must use the highly effective methods of contraception (or true sexual abstinence when in line with the preferred and usual lifestyle of the participant) as described in section 8.2 and 8.4. Based on its mechanism of action (PARP inhibition), olaparib could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 400 mg twice daily.

Patients who become pregnant during the trial must be withdrawn immediately. The Investigator must make every effort to try and ensure that a clinical trial patient, who is fertile, does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and providing each patient with information about appropriate medically approved contraception.

13.8.1 Contraception

Paclitaxel, cediranib, and olaparib in this trial have a demonstrated or suspected human teratogenicity/fetotoxicity. Women of Childbearing Potential (WOCP) entering this trial must agree to use highly effective methods of contraception for four weeks before joining the trial, throughout the trial and for six months after completing the trial treatment. For the list of acceptable contraceptive methods see the exclusion criteria in section8.2.

13.8.2 Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy,

it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

The Investigator should report pregnancy occurring within SAE reporting periods stipulated in the trial protocol (for example, some trial protocols may state that SAEs should be reported during the trial treatment period and up to 30 days after the last date of treatment, this timeline would also apply to the reporting of pregnancies). Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

13.9 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the MHRA and Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

14 Statistical considerations

14.1 Sample size

The main objective of the trial is to establish that the treatment combination with paclitaxel and cediranib is safe and will not result in an unacceptable number of patients experiencing bowel perforation or fistula. A previous study in ovarian cancer found that the GI perforation rate was 23.8% in patients treated with bevacizumab who had received more than 3 lines of chemotherapy, therefore the GI perforation-free rate in this study was 76.2%. This trial will assess the GI perforation rate in ovarian cancer patients who are also at high risk of developing GI perforation.

We have utilised a Simon's two-stage design to incorporate a planned check of the number of perforation and fistula events in a small number of patients before recruiting all patients into the trial. This will allow the trial to be stopped early if the rate of events is unacceptable.

We expect that on the new cediranib-paclitaxel/nab-paclitaxel combination, 96% of participants will be free of bowel perforation or fistula, but we would not pursue the combination further if fewer than 76.2% of patients are perforation/fistula-free. With 90% power and 5% significance, we will require 10 participants to be recruited into stage 1. When the 10th participant has been recruited and followed up for six weeks after starting cediranib treatment, the number of patients free of perforation/fistula events will be reviewed by the IDMC. If at least 9 participants are free of perforation/fistula events, the trial will continue to stage 2, and a further 14 patients will be recruited. If at least 22 participants are free of perforation/fistula events by the end of the trial period, then we will conclude that the treatment is safe. If 3 or more participants experience an event at any point in the trial, then no more participants will be recruited. Given the expected recruitment rate of 1.25 participants per month, it will not be necessary to suspend recruitment after the 10th participant is registered, if no bowel perforations or fistulas are reported in the first 9 participants. Additional participants will be recruited as a contingency to replace those who are not assessable for the primary endpoint if they do not receive cediranib or withdraw consent from the trial before perforation events can be assessed.

14.2 Missing, unused & spurious data

We will ask the site to confirm whether each participant has had a perforation or fistula event six weeks after stopping cediranib, or at the point of analysis if they are still on cediranib treatment.

We do not expect missing data for the primary outcome and there will be no data imputation for missing data in the primary endpoint. Imputation methods for missing data in the secondary endpoints will be fully documented in the SAP. There may be some un-evaluable participants who do not receive cediranib. A replacement participant will be recruited in this situation.

Time to event data will be censored at the date the participant was last seen if no event is recorded during the trial.

14.3 Procedures for reporting deviation(s) from the original SAP

Any deviation(s) from the final statistical plan will be described and justification given in the final report.

14.4 Termination of the trial

As described in section 14.1, the trial may terminate early if >1/10 participants in stage 1 or >2 participants in the whole trial experience a primary endpoint event. The trial may also be terminated for other safety reasons if recommended by the IDMC and agreed by the TSC. IDMC membership, meeting schedule, communication plan, and other operational details are described in the IDMC Charter.

14.5 Inclusion in analysis

All participants who start cediranib and receive at least 5 days' treatment will be included in the primary endpoint safety analysis.

The Intention-to-Treat (ITT) population will be the basis for analysis of secondary endpoints in this study and will constitute all registered subjects.

15 Analysis

15.1 Main analysis

15.1.1 *Safety analysis*

The proportion of patients who are free of bowel perforation or fistulas related to cediranib treatment (primary analysis) will be calculated with an exact 95% confidence interval (CI) calculated using the Clopper-Pearson method.

In addition, analyses will consist of the proportion of patients developing bowel obstruction (defined as hospital admission for bowel obstruction reported as an SAE) and the proportion developing grade III or more AEs. AEs will be coded using CTCAE version 4.03 terminology, which maps directly to the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be summarised by severity, toxicity and timing (baseline and worst toxicity reported overall and in Component 1 and Component 2). SAEs, SARs and SUSARs will be summarised by severity, toxicity type, causal relationship to study drug(s) and by timing with respect to whether during Component 1 or Component 2. SAE line listing by patient will also be presented. Figures will be presented to show the percentage of each adverse event experienced of any grade and Grade 3+ experienced by treatment in Components 1 and 2 and the number of adverse events experienced per patient in Components 1 and 2, of any grade and Grade 3+. A further figure will show the percentage of toxicities for those experienced in more than 10% of patients, as a stacked bar chart colour-coded for Grades 1/2 and Grades 3+ by treatment.

15.1.2 Treatment compliance

The median relative dose intensity (calculated as detailed in Section 5.4) of paclitaxel/nab-paclitaxel, cediranib and olaparib will be summarised with the interquartile range (IQR). The median duration and IQR of cediranib treatment will also be summarised. Median doses (with IQR), dose reductions (N(%)) and dose delays (N(%)) of paclitaxel/nab-paclitaxel, cediranib and olaparib will be summarised by cycle.

15.2 Efficacy Analysis

The Intention-to-Treat (ITT) population will be the basis for the analysis of PFS and OS in this study.

The ORR (participants demonstrating either complete response or partial response within the first 18 weeks) will be summarised as the proportion of patients with objective response with an exact 95% confidence interval.

PFS and OS will be summarized descriptively using the Kaplan-Meier method. Progression will be defined as radiological progression as determined by RECIST 1.1 or clinical progression if this is reported on a RECIST CRF. Median PFS will be estimated from the 50th percentile of the corresponding Kaplan-Meier estimate.

15.3 Exploratory Analysis

The proportion of participants with prior treatment with bevacizumab will be summarised. Toxicities, ORR, PFS and OS will be summarised for participants per bevacizumab group.

In participants, whose disease progresses and who switch to olaparib-cediranib, Grade III or more toxicities (including bowel perforations and fistulas occurring after the switch) will be summarised. Additionally, the proportion of patients with pathogenic germline BRCA 1 or 2 mutations will be calculated and Grade III or more toxicities, ORR, PFS and OS will be summarised for participants per BRCA mutational status. The ORR and median time from switching to cediranib + olaparib until further progression will also be calculated.

Vital signs data will be summarised by changes from baseline values using descriptive statistics. Laboratory parameters, ECOG and ECG data will also be summarised using descriptive statistics.

15.4 Interim Analysis

There is one planned analysis; six weeks from when the 10th participant starts cediranib, and a final analysis after all participants that start cediranib treatment have received treatment for at least 18 weeks or have withdrawn or died up to 18 weeks and are evaluable for the primary outcome. Only participants that receive at least 5 days of cediranib will be included in the analysis population for the primary outcome.. It is proposed that recruitment will continue whilst awaiting outcome of interim analysis, if no perforation or fistula events have been reported. The IDMC will also review the safety data at least on a yearly basis if recruitment is slower than anticipated.

16 Data Management

A paper CRF will be used to collect the data. The PI is responsible for ensuring the accuracy, completeness, legibility of the data reported in the CRFs. Only the Investigator and those personnel who have signed the Delegation Log provided by the CTR and have been authorised by the Investigator should enter or change data in the CRFs. All protocol required investigations must be reported in the CRF. The Investigators must retain all original source data reports, traces and confirming agreement with University of Manchester to ensure that:

- Sufficient data are recorded for all participating patients to enable accurate source document verification between hospital records and CRFs.
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits.
- Trial-related monitoring, audits are permitted and direct access to source data/documents is provided as required.

Once the participant is 'off trial' and the CRF has been fully completed, the Investigator must provide a signature to authorise the completed CRF for that participant. At the end of the trial all paper CRFs are retained and archived by the CTR.

Trial data	Source data

	Consent form	CRF	Medical notes / GP letter	Participant diary	Pharmacy file
Written informed consent	X				
Demographics		X			
Medical history			X		
Pregnancy test			X		
ECOG Performance status		X			
Physical Examination		X			
Vital signs – blood pressure and temperature		X			
Urine dipstick			X		
Safety bloods			X		
Full Blood Count			X		
RECIST v1.1 reporting			X		
Adverse event and toxicity evaluation		X			
Concomitant treatments/medications			X		
Overall survival			X		
ECG			X		
Trial medication dispensed					X

16.1 Completion of Paper CRFs

The top copy of each completed CRF should be returned to the CTR for data entry within four weeks of the visit. The remaining copy is to be retained at the local site. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

CRF pages and data received by the CTR from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to respond to the data query on the data clarification form. The case report form pages should not be altered.

All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the CTR and a copy retained at the site along with the participants' CRFs.

The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

17 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

18 End of Trial definition

The treatment phase will be followed by a 28-day follow-up period which will continue for 28 days after the last participant completes protocol treatment.

The end of the trial is defined as the date of final data capture to meet the trial endpoints.

Sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

19 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 25 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The PI is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

20 Regulatory Considerations

20.1 CTA

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority: MHRA.

20.2 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review dependant on the location of the lead site e.g. DSCHR PCU if Wales led and HRA if English led.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

20.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian and the translational sample custodian for this trial is the CTR

20.4 Indemnity

The University of Manchester will act as the sponsor for this trial. Delegated responsibilities will be assigned to the CTR to manage the trial on behalf of the Sponsor, and to participating sites recruiting patients into this trial. All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site.

The University of Manchester has a specialist insurance policy in place for research involving human participants that provides cover for legal liabilities arising from its actions or those of its staff or supervised students, subject to policy terms and conditions.

The manufacturer supplying the IMP has accepted limited liability related to the manufacturing and original packaging of the trial drug and to the losses, damages, claims or liabilities incurred by trial participants based on known or unknown AEs which arise out of the manufacturing and original packaging of the trial drug, but not where there is any modification to the trial drug (including without limitation re-packaging and blinding).

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

20.5 Trial sponsorship

University of Manchester will act as the sponsor for this trial. Delegated responsibilities will be assigned to the CTR to manage the trial on behalf of the sponsor and to the participating sites recruiting patients into this trial.

The University shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005).
- The General Data Protection Regulation 2018.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The Sponsor has delegated certain responsibilities to Cardiff University (CTR), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

20.6 Funding

This trial is funded by AstraZeneca and who are also providing trial drug (cediranib and olaparib).

21 Trial management

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial

21.1 TMG (Trial Management Group)

A TMG will be established and will include those individuals responsible for the day-to-day management of the trial including the CI, co-investigators and identified collaborators, PIs, the trial statistician and the TM. Where possible, membership will include a lay/consumer representative.

Notwithstanding the legal obligations of the Sponsor and CI, the TMG have operational responsibility for the conduct of the trial including monitoring overall progress to ensure the protocol is adhered to and to take appropriate action to safeguard the patients and the quality of the trial. The TMG will meet at least every 3 months once the trial is actively recruiting. Minutes will be taken at TMG meetings and copies of the minutes will be filed in the TMF. The TM and CI will ensure that all relevant issues and actions discussed during the meeting are followed up and resolved and details of significant issues will be made available to participating sites. Minutes of all TMG meetings are available on request.

TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

21.2 TSC (Trial Steering Committee)

A TSC will be established and will include an independent Chairman (not involved directly in the trial other than as a member of the TSC), not less than two other independent members, a representative from a consumer group, plus the CI, one or two PIs, the TM and statistician.

The role of the TSC is to take responsibility for the scientific integrity of the trial, the scientific validity of the trial protocol, assessment of the trial quality and conduct (to ensure that the trial is being conducted in accordance with the principles of GCP and the relevant regulations) as well as for the scientific quality of the final trial report. Decisions about the continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

The TSC will meet once ethics approval has been given and before the trial begins recruitment. Once the trial has started the TSC should meet at least annually to monitor the progress of the trial although there may be periods when more frequent meetings are necessary. Meetings should be organised by the CI via the TM. Minutes will be taken at TSC meetings and copies of the minutes will be filed in the Trial Master File. The TM and CI will ensure that all relevant issues and actions discussed during the meeting are followed up and resolved and details of significant issues will be made available to participating sites. Minutes of all TSC meetings are available on request. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by the CTR.

21.3 Independent Data Monitoring Committee (IDMC)

An IDMC will be instigated to review accruing trial data and to assess whether there are any safety issues that should be brought to the participant's attention, whether any safety amendments should be made or if there are any reasons for the trial should not continue. The IDMC will be independent of the investigators, funder and sponsor and will comprise of a statistician and at least 2 other experts in the disease area under investigation. The CI and TMG with the support of the CTR will be responsible for nominating IDMC members. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by CTR. This charter will outline any stopping rules and the frequency of analysis and IDMC meetings frequency during the trial. The IDMC will meet in confidence at regular intervals.

Reports to the IDMC will be prepared and presented by the trial statistician and TM prior to the IDMC meeting. The IDMC Chairman will then report their recommendations to the Chairman of the TSC or TMG and may request additional reports or information if required. This report will be submitted to the TMG and TSC, and if required, the REC and the MHRA and the CI and TM will ensure that all actions and recommendations are followed up.

IDMC members will be required to sign up to the remit and conditions as set out in the DMC Charter.

22 Quality Control and Assurance

22.1 Monitoring

The clinical trial risk assessment will be used to determine the intensity and focus of central and on-site monitoring activity in the CEBOC trial. A trial monitoring plan will be in place and fully documented before the trial opens to recruitment.

The monitoring plan will be developed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products'. Due to the Type C risk associated with the IMP a higher intensity monitoring plan will be employed, with additional monitoring if required to address specific vulnerabilities identified in the risk assessment.

Site investigators will permit trial related monitoring by providing direct access to source data and documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PIs and local R&D departments.

22.2 Audits & inspections

The trial is participant to inspection by MHRA as the regulatory body. The trial may also be participant to inspection and audit by University of Manchester under their remit as Sponsor.

The site must inform the CTR of any MHRA inspections.

23 Publication policy

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the TMG, and high accruing clinicians. All participating centres and clinicians will be acknowledged in this publication together with staff from the CTR. All presentations and publications relating to the trial must be authorised by the TMG and sponsor, on whose behalf publications should usually be made. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the CEBOC trial without prior permission from the TMG and sponsor.

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25 Appendices

25.1Appendix 1: WHO / ECOG Performance Status

0 Asymptomatic (fully active, able to carry on all pre-disease activities without restriction).

1 Symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; for example, light housework, office work).

2 Symptomatic, < 50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours).

3 Symptomatic, > 50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours).

4 Bedbound (completely disabled, cannot carry on any self-care, totally confined to bed or chair).

5 Death.

25.2 Appendix 2: RECIST v1.1

All patients will have their BEST RESPONSE on study classified as outlined below. Note that in CEBOC scans will not be required for confirmation of response as the primary endpoint is the feasibility of two cycles of olaparib. The best response as defined below should be used.

- ***Complete Response***: Disappearance of all target and non-target lesions including normalization of elevated tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis).
- ***Partial Response***: At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
- ***Stable Disease***: Steady state of disease; neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters of target lesions while on study. For nonrandomized studies, stable disease must be documented as present at least 4 weeks from the start of the therapy. There may be no appearance of new lesions for this category.
- ***PD***: At least a 20% increase (and an absolute increase of at least 5 mm) in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of PD.
- ***Non-CR/Non-PD***: Persistence of 1 or more non-target lesions and/or maintenance of tumour marker level above the normal limits.

Table 1: summary of RECIST v1.1 Response Criteria

Target Lesions	Non-target Lesions	New Lesions	Overall response	Best response for this category also requires
CR	CR	No	CR	≥ 4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Not –PD or not all evaluated	No	PR	

SD	No- PD or not at all evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	No-PD	No	NE	NE
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD NE- non-evaluable Not: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at the time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.				

Table 2: time point response: Patients with non-target disease only

Target Lesions	Nontarget Lesions	New Lesions	Overall response	Best response for this category also requires
CR	CR	No	CR	≥ 4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Not –PD or not all evaluated	No	PR	
SD	No- PD or not at all evaluated	No	SD	Documented at least once

				≥ 4 weeks from baseline
Not all evaluated	No-PD	No	NE	NE
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

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

NE- non-evaluable

Not: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at the time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 3: Best overall response when confirmation of CR and PR required

Overall Response First timepoint	Overall Response Subsequent timepoint	Best overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

CR	NE	SD provided minimum criteria for SD duration met, otherwise, PD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, PD
NE	NE	SD provided minimum criteria for SD duration met, otherwise, PD

NE= non-evaluable

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