ARCAGY - GINECO

A Randomized Study of Paclitaxel – Carboplatin followed by maintenance Niraparib versus Paclitaxel – Carboplatin – Bevacizumab followed by maintenance Niraparib + Bevacizumab in Patients With Advanced Ovarian, Fallopian Tube or Primary Peritoneal Cancer Following a Front-Line Complete Cytoreduction Surgery

NIRVANA-1 SYNOPSIS

GINECO-OV129b / ENGOT-OV63		EudraCT N° 2021-002095-39
Development Phase: Phase II		Subject: Ovarian cancer
Version 0.11	**03 MAY 2021**	TREATMENT : Paclitaxel/Carboplatin+Niraparib Paclitaxel/Carboplatin/Bevacizumab+Niraparib/Bevacizumab

Coordinating Investigator:	***Pr Gilles FREYER, MD, PhD*** Service d'Oncologie Médicale Centre Hospitalier Lyon-Sud 69495 Pierre-Bénite CEDEX France Phone: : +33 4 78 86 43 18 E-mail : gilles.freyer@univ-lyon1.fr
Scientific coordinator:	***Pr Isabelle RAY-COQUARD, MD, PhD*** Centre Léon Bérard 28, rue Laennec 69373 Lyon cedex 08 France Phone: +33 4 78 78 28 88 Email: isabelle.ray-coquard@lyon.unicancer.fr
Biostatistician:	***Bernard ASSELAIN*** Comité Statistique du GINECO 8 rue Lamennais 75008 PARIS Phone : + 33 (0) 6 15 08 46 26 E-mail : b.asselain@gmail.com
Project Manager:	***Aurélie CHABANON*** ARCAGY-GINECO 8, Rue Lamennais 75008 PARIS Phone: + 33 (0)1 84 85 20 36 Fax: + 33(0)1 43 26 26 73 E-mail: achabanon@arcagy.org
Sponsor:	**ARCAGY-GINECO** 8, Rue Lamennais 75008 PARIS France

PROTOCOL SUMMARY

GENERAL INFORMATION	
TITLE	A Randomized Study of Paclitaxel – Carboplatin followed by maintenance Niraparib versus Paclitaxel – Carboplatin – Bevacizumab followed by maintenance Niraparib + Bevacizumab in Patients With Advanced Ovarian, Fallopian Tube or Primary Peritoneal Cancer Following a Front-Line Complete Cytoreduction Surgery
STUDY DESIGN	Phase II, randomized, open label, multi-centre study to assess the efficacy niraparib versus niraparib +bevacizumab maintenance in patients with newly diagnosed stage IIIA/B/C high-grade epithelial ovarian cancer with no residual disease after frontline surgery and treated by adjuvant platinum-based chemotherapy +/- bevacizumab.
THERAPEUTIC INDICATION	Ovarian cancer
STUDY IDENTIFICATION	NIRVANA-1 GINECO-OV129b / ENGOT-OV63
SPONSOR	ARCAGY - GINECO
COORDINATING INVESTIGATOR	Pr Gilles FREYER
COOPERATIVE GROUP	GINECO (France), and 6 others group (TBD)
VERSION / DATE	**Version 0.11, 03May2021**
STUDY OBJECTIVES	
Objectives	Primary Objectives: • Progression-free survival rate at 24 months Secondary Objectives: • Progression Free Survival • Progression Free Survival 2 (PFS2) • Safety of maintenance niraparib + bevacizumab in first line. • Assessment of the long-term overall survival (5 years) in both arms. • Time to First Subsequent Treatment • Time to Second Subsequent Treatment • Confirmation of the predictive value (overall chemo-sensitivity) of the KELIM
Endpoint	Primary Endpoint:

	• Progression-free survival (PFS) is defined as time from randomization until objective tumor progression or death, whichever occurs first. Secondary Endpoints: • PFS2 is defined as time from randomization to objective tumor progression on next-line treatment or death from any cause. • Safety assessed based on CTCAE version 5 • OS will be defined as the number of days from the day the subject is randomized to the date of the subject's death. • TFST is defined as the time from the date of randomization to date of the first subsequent anticancer therapy or death • TSST is defined as the time from the date of randomization to the earlier of the date of second subsequent chemotherapy start date, or death date. • KELIM assessed on repeated CA-125 assay
METHODOLOGY	
DESIGN	Phase II, randomized, open label, multi-centre study. Randomization on a 1:1 ratio, stratification performed according to: • BRCA status (local assessment) • FIGO stage at diagnosis (IIIA versus IIIB/IIIC) • Previous hyperthermic intraperitoneal chemotherapy (yes/no).
NUMBER OF PATIENTS / SAMPLE SIZE	The study was calibrated to detect a treatment effect corresponding to a 24-months PFS rate of 75% in the niraparib plus bevacizumab arm and a 24-months PFS rate of 65% in the niraparib alone arm, translating in a hazard ratio of 0.67, with a 1:1 randomization. Given the highest benefit observed for CC-0 patients in the PAOLA 1 study, the HR of 0.65 in the overall population of the PRIMA trial, and the 50 % PFS rate at 24 months in the LION trial [1]– where all patients had upfront surgery with no residual disease – our estimation in the absence of previously reported data in the specific subpopulations of the Nirvana-1 trial seems reasonable. According to the Freedman method (Stat in Med, 1982), A **total of 110 events in the study** would provide a 80% power to show statistically significant PFS accepting a 1-sided alpha risk of 10%. Considering minimal follow-up of 24 months, and assuming a total dropout rate of 5%, **390 patients are to be randomized in the study**. No efficacy interim analysis will be carried-out before the final analysis.
INCLUSION CRITERIA	For inclusion in the study, patient should fulfill the following criteria:

	1. Female patient ≥ 18 years of age. 2. Signed informed consent and ability to comply with treatment and follow-up. 3. Patient with newly diagnosed, a. Ovarian cancer, primary peritoneal cancer and/or fallopian-tube cancer, b. Histologically confirmed (based on local histopathological findings): • high grade serous or • high grade endometrioid (grade 2 and 3) or • other epithelial non mucinous and non-clear cell ovarian cancer in a patient with germline BRCA 1 or 2 deleterious mutation c. At an advanced stage: FIGO stage IIIA to IIIC of the 2018 FIGO classification. 4. Patient having undergone frontline, complete cytoreductive surgery (i.e. no visible residual disease): The patient will be considered eligible once the ESGO Quality Assurance in Ovarian Cancer Surgery will have been filled out and validated 5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. 6. Patient must have received one cycle of carboplatin AUC 5-6 + paclitaxel 175 mg/m² 7. Patient must have started cycle 1 chemotherapy no later than 6 weeks after surgery. 8. Patient must have a thorax-abdomen-pelvis CT scan between surgery and Cycle 1, with no evidence of disease. 9. Patient eligible for first line platinum-taxane chemotherapy: 10. Patient eligible for bevacizumab treatment in combination with chemotherapy and in maintenance. It must be started at the second chemotherapy cycle and be administered at a dose of 15mg/kg every 3 weeks up to a total of 15 months. 11. Patient must have normal organ and bone marrow function before first cycle of chemotherapy: • Hemoglobin ≥ 9.0 g/dL. • Absolute neutrophil count (ANC) ≥ 1.5 x 109/L. • Platelet count ≥ 100 x 109/L. • Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN).

	• Aspartate aminotransferase/Serum Glutamic Oxaloacetic Transaminase (ASAT/SGOT)) and Alanine aminotransferase /Serum Glutamic Pyruvate Transaminase (ALAT/SGPT)) ≤ 2.5 x ULN • Serum creatinine ≤ 1. 5 x institutional ULN and GFR > 50 mL/min, by using an exact measure (ie. Iohexol clearance) or the most appropriate formula (Jeliffe, Cockroft Gault, MDRD, CKD-EPI) to the investigator's discretion. • Patient not receiving anticoagulant medication who has an International Normalized Ratio (INR) ≥1.5 and an Activated ProThrombin Time (aPTT) ≥1.5 x ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or APTT is within therapeutic limits (according to site medical standard). If the patient is on oral anticoagulants, dose has to be stable for at least two weeks at the time of randomization. 12. Urine dipstick for proteinuria < 2+. If urine dipstick is ≥2+, 24-hour proteinuria must be <1 g 13. Normal blood pressure or adequately treated and controlled hypertension (systolic BP ≤ 140 mmHg and/or diastolic BP ≤ 90 mmHg). 14. Formalin fixed paraffin embedded (FFPE) tumor sample from the primary cancer must be available for local BRCA testing and if possible HRD testing (optional). 15. For countries where this will apply to: a subject will be eligible for randomization in this study only if either affiliated to, or a beneficiary of a social security category.
EXCLUSION CRITERIA	1. Patient with clear cell adenocarcinoma or carcinosarcoma, non-epithelial origin of the ovarian tumor, the fallopian tube or the peritoneal tumor (i.e. germ cell tumors). 2. Ovarian tumor of low malignant potential (e.g. borderline tumor), or mucinous carcinoma. 3. Patient with a diagnosis, detection, or treatment of another type of cancer ≤ 2 years prior to initiating protocol therapy (except basal or squamous cell carcinoma of the skin and cervical cancer in situ that has been definitively treated and synchronous grade 1 stage 1 endometrial cancer) *Patient with history of primary triple negative breast cancer may be eligible provided she completed her definitive anticancer treatment more than 3 years ago and she remains breast cancer disease free prior to start of study treatment.*Patient with

	synchronous high grade serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium is not eligible. 4. Patient with myelodysplastic syndrome/acute myeloid leukemia history 5. Patient receiving radiotherapy within 6 weeks prior to study treatment 6. Previous allogenic bone marrow transplant. 7. Any previous treatment with PARP inhibitor. 8. Administration of other simultaneous chemotherapy drugs – except during a HIPEC procedure with cisplatin at PDS -, any other anticancer therapy or anti-neoplastic hormonal therapy, or simultaneous radiotherapy during the trial treatment period (hormonal replacement therapy is permitted as are steroid antiemetics). 9. Current or recent (within 10 days prior to randomization) chronic use of aspirin > 325 mg/day. 10. Prior history of hypertensive crisis (CTC-AE grade 4) or hypertensive encephalopathy. 11. Clinically significant (e.g. active) cardiovascular disease, including: • Myocardial infarction or unstable angina within ≤ 6 months of randomization, • New York Heart Association (NYHA) ≥ grade 2 congestive heart failure (CHF). • Poorly controlled cardiac arrhythmia despite medication (patient with rate controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on resting ECG, • Peripheral vascular disease grade ≥ 3 (e.g. symptomatic and interfering with activities of daily living [ADL] requiring repair or revision). 12. Previous Cerebro-Vascular Accident (CVA), Transient Ischemic Attack (TIA), Sub- Arachnoids Hemorrhage (SAH) or Posterior Reversible Encephalopathy Syndrome (PRES) within 6 months prior to randomization. 13. History or evidence of hemorrhagic disorders within 6 months prior to randomization. 14. Evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation). 15. History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory (within 4 weeks prior to randomization) in case of suspected brain metastases.

	Spinal MRI is mandatory (within 4 weeks prior to randomization) in case of suspected spinal cord compression. 16. History or evidence upon neurological examination of central nervous system (CNS) disease, unless adequately treated with standard medical therapy (e.g. uncontrolled seizures). 17. Significant traumatic injury during 4 weeks prior to randomization. 18. Non-healing wound, active ulcer, or bone fracture. Patient with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection is eligible but require 3 weekly wound examinations. 19. History of VEGF therapy related abdominal fistula or gastrointestinal perforation or active gastrointestinal bleeding within 6 months prior to the first study treatment. 20. Current, clinically relevant bowel obstruction, including sub-occlusive disease, related to underlying disease. 21. Patient with evidence of abdominal free air not explained by paracentesis or recent surgical procedure. 22. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment related complications. 23. Pregnant or lactating women. 24. Participation in another clinical study with any intravenous or oral investigational product is not allowed. However, participation in a surgical clinical study including Hyperthermic Chemotherapy (HIPEC) during the surgical procedure is allowed. 25. Patient unable to swallow orally administered medication and patient with gastrointestinal disorders likely to interfere with absorption of the study medication. 26. Patient with a known contraindication or uncontrolled hypersensitivity to the components of paclitaxel, carboplatin, niraparib, bevacizumab, or their excipients. 27. Immunocompromised patient, e.g., with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids or patient who is known to be serologically positive for human immunodeficiency virus (HIV). 28. Participant has a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to uncontrolled major

	seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent
STUDY TREATMENT OUTLINE	
Description of Study Agent/Study Procedure:	**Treatment**: Chemotherapy (Paclitaxel/Carboplatin), Niraparib, Bevacizumab This trial entails the following phases: Screening, Run-in period, chemotherapy treatment, maintenance treatment and Follow-Up visits. <u>Screening period:</u> Screening procedures have to be completed within 28 days prior to Cycle 1 Day 1 (C1D1) of the Chemotherapy Run-In Period. <u>Run-In Period</u>: Prior to randomization, all patients will receive 1 cycle of paclitaxel-carboplatin during a Chemotherapy Run-In Period. Patients will be randomized following Cycle 1, prior to treatment in Cycle 2 during the Chemotherapy Treatment Period. Randomization must be performed after cycle 1 chemotherapy, and within 3 business days prior to C2D1. All screening procedures are to be performed and patient eligibility is to be confirmed prior to randomization. Depending on the arm of randomization, patients is subject to receive bevacizumab. Bevacizumab must not be administered less than 28 days following major surgery, and post-operative incisions must be fully healed. <u>Treatment (including chemotherapy and maintenance)</u>: **- Arm A:** carboplatin AUC 5-6 + paclitaxel 175 mg/m² q3w, 5 cycles, followed by niraparib$^{\Delta}$ 200* or 300 mg/d for 2 years. **- Arm B**: carboplatin AUC 5-6 + paclitaxel 175 mg/m² + bevacizumab 15 mg/kg q3w, 5 cycles, followed by bevacizumab 15 mg/kg q3w for 15 months + niraparib$^{\Delta}$ 200* or 300 mg/d for 2 years. $^{\Delta}$ *Eligibility to maintenance therapy is to be confirmed prior to first niraparib administration* ** Patients < 77 kg and/or platelets < 150 G/l, as measured prior to dosing at D1 of the Maintenance Treatment Period, will receive niraparib 200 mg/d* <u>End of Treatment and follow up visits</u>: Assessments to be performed within 30 days of last administration. After completing the End-of-Treatment visit, all patients will enter the Follow-Up phase. Visits will be performed every 3 months +/- 10 days, beginning 3 months after the last intake of niraparib. PFS, PFS2, overall survival and subsequent anti-cancer therapies will be collected at each visit, when applicable.

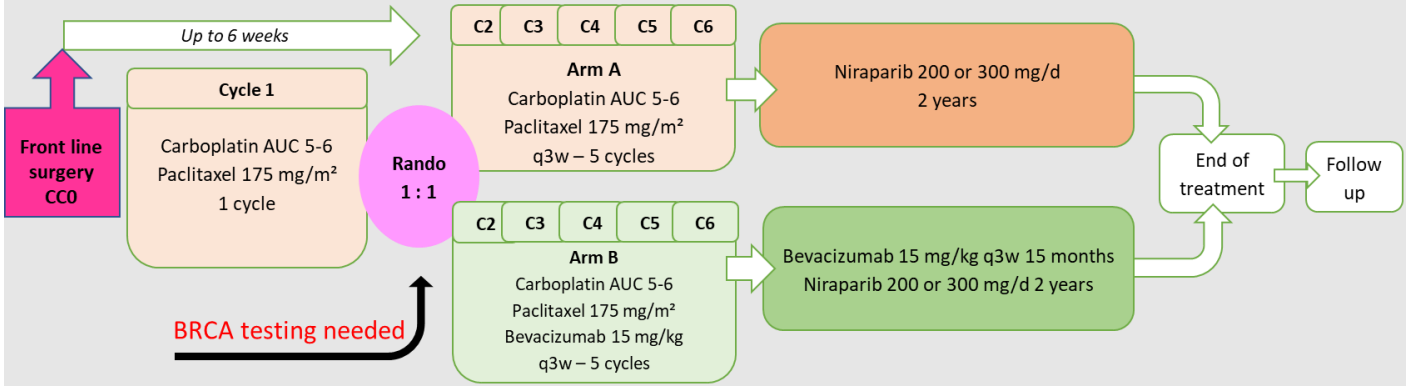
STUDY COMMITTEES	**Data Safety Monitoring Committee (DSMB)** An Data Safety Monitoring Committee Board (DSMB) will be established for the NIRVANA-1 trial. It will be constituted by the sponsor and will be composed of statisticians and clinical experts. The DSMB will meet on a regular basis and will be responsible for independently evaluation of the safety for the patients participating in the clinical trial. DSMB will make recommendations concerning the conduct of the trial to the sponsor ARCAGY-GINECO especially whether it is safe to continue the enrolment as planned. The DSMB will regularly review AEs, SAEs including toxicity of interest such as MDS, AML and new primary cancer all along the trial. The DSMB will also check the integrity and the validity of the data and the conduct of the clinical trial. The responsibilities of the DSMB will be documented in a separate Charter. **Steering committee** A Steering Committee will be composed of Sponsor representatives, the International Coordinating Investigator, the Principal Investigator of each participating country involved in the study, and other external participants, as needed. The Steering Committee has primary responsibility for the general organization of the trial and makes any major decision recommended by the DSMB. A first meeting is scheduled after the first DSMB meeting. Additional meetings may be called at any time on request by one or more members. They will meet regularly in person or by phone to review the progress of the study within all clinical centres including recruitment, problems with protocol compliance, unexpected toxicities and need for protocol amendments.
Number of Sites enrolling participants:	Approximatively 100
Estimated Study Duration:	Estimated First Patient First Visit: Q4 2021 Estimated Last Patient First Visit: Q4 2023 Estimated Last patient Last Treatment: Q1 2026

STUDY DESIGN

- Stage IIIA/B/C
- High-grade non-mucinous and non-clear cell epithelial ovarian, fallopian tube or primary peritoneal carcinoma
- Complete cytoreduction
- BRCA status mandatory
- PS 0/1

STRATIFICATION

- BRCA status (local assessment)
- FIGO stage at diagnosis (IIIA versus IIIB/IIIC).
- Previous hyperthermic intraperitoneal chemotherapy (yes/no).



FLOWCHART

SCREENING AND CHEMOTHERAPY PHASE	Screening	REGISTRATION	Run in period		RANDOMIZATION [13]	Chemotherapy				
	Between surgery and C1		C1D1	Within 7 days prior randomization		C2D1	C3D1 (Q3W)	C4D1 (Q3W)	C5D1 (Q3W)	C6D1 (Q3W)
	Up to 6 weeks						*+/- 3days*	*+/- 3days*	*+/- 3days*	*+/- 3days*
Informed consent	X									
BRCA testing	X									
Medical & Cancer History	X									
Demographics	X									
Physical examination	X		X[1]	X		X[1]	X	X	X	X
ECOG Performance Status	X		X[1]	X		X[1]	X	X	X	X
Vital signs[15]	X		X[1]	X		X[1]	X	X	X	X
ECG	X		*If clinically indicated*			*if clinically indicated*				
Hematology[18]	X		X[1]	X		X[1]	X	X	X	X
Serum biochemistry[18]	X		X[1]	X		X[1]	X	X	X	X
Coagulation[18]	X		X[1]	X		X[1]	*If clinically indicated*			
Urinalysis including proteinuria	X			X		X[1, 2, 5]	X[2, 5]	X[2, 5]	X[2, 5]	X[2, 5]
CA-125	X			X		X[1]	X	X	X	X
Tumor Assessment [14]	X									
ESGO Questionnaire	X									
Chemotherapy administration[3]			X			X	X	X	X	X
Bevacizumab administration[4, 5]						X	X	X	X	X
Blood samples (serum)	X					X			X	
Tissue sample	X									
Adverse events						X	X	X	X	X
Concomitant medications[6]	X		X			X	X	X	X	X

MAINTENANCE PHASE	Maintenance (Q3W +/- 3days)																					
	Visit 1	Visit 2&3	Visit 4	Visit 5&6	Visit 7	Visit 8&9	Visit 10	Visit 11&12	Visit 13	Visit 14&15	Visit 16	Visit 17&18	Visit 19	Visit 20&21	Visit 22	Visit 23&24	Visit 25	Visit 26&27	Visit 28	Visit 29&30	Visit 31	Visit 32&33	Visit 34
Type of visit[16]	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site	TC/ On site	On site
From start of maintenance	W1		W10		W19		W28		W37		W46		W55		W64		W73		W82		W91		W100
From start of chemotherapy	W19		W28		W37		W46		W55		W64		W73		W82		W91		W100		W109		W118
Informed consent																							
Maintenance therapy eligibility assessment[20]	X																						
Physical examination	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X
Vital signs[15]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X	X[17]	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	*Periodically*										
Heart rate	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	*Periodically*										
Hematology[18]	X[19]	X[19]	X	X	X		X		X		X		X		X		X		X		X		X
Serum biochemistry[18]	X	X	X	X	X		X		X		X		X		X		X		X		X		X
ECG	*If clinically indicated*																						
Coagulation[18]	*If clinically indicated*																						
Urinalysis[5]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	*If clinically indicated*							
CA-125	X[8, 9]		X		X		X		X		X		X		X		X		X		X		X
Blood samples (serum)	X[8]		X		X		X		X		X		X		X		X		X		X		X
Tumor Assessment [14]	X	*Every 18 weeks (+/-1week) from start of maintenance and until 2 years from date of randomization, then at investigator's discretion – Additional imaging is indicated in case of CA 125 increase (GCIG criteria)*																					
Assess for MDS/AML[21]	*If clinically indicated*																						
Bevacizumab adm. [4, 5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Niraparib adm.[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X																						
Concomitant medications[6]	X																						

END OF TREATMENT AND FOLLOW UP	End of treatment[11]	Follow up[12]		
	Within 30 days of last administration	Up to PFS1	Up to PFS2	Survival
		Every 4 months +/- 10d		
Informed consent				
Physical examination	X	X	X	X
ECG	X	X	X	X
Vital signs[15]	X	X	X	X
ECG	*If clinically indicated*			
Hematology[18]	X			
Coagulation[18]	*If clinically indicated*			
Serum biochemistry[18]	X			
Urinalysis[5]	X			
CA-125	*If clinically indicated*	X	*If clinically indicated*	
Blood samples (serum)		X		
Tumor Assessment [14]	*Every 18 weeks (+/-1week) from start of maintenance and until 2 years from randomization, and then at investigator's discretion - Additional imaging is indicated in case of CA 125 increase (GCIG criteria)*			
Assess for MDS/AML [21]	*If clinically indicated*			
Adverse events	X			
Concomitant medications[6]	X			
New anticancer therapy			X	X

[1] To be repeated if they have not been done within 10 days (7 days prior to randomization and 3 days between randomization and C2D1)

[2] To be performed during bevacizumab treatment. After bevacizumab treatment discontinuation if clinically indicated

[3] Carboplatin AUC 5-6 + paclitaxel 175 mg/m² q3w

[4] 15 mg/kg, in combination with chemotherapy + in maintenance for 15 months in total.

[5] For patient in arm B only

[6] From 30 days prior to ICF signature up to the end of treatment

[7] Blood pressure and heart rate should be monitored weekly for first 2 months (9 weeks) of maintenance, then every 3 weeks (at each visit) for first year, and periodically thereafter.

[8] Before the start of niraparib maintenance therapy

[9] CA-125 to be performed at each cycle during chemotherapy and then every 3 cycles/9 weeks from start of maintenance (C7D1, C10D1, C11D1, C16D1…).

[10] For patient in both arms, Niraparib capsules will be administered orally QD continuously (in 21-day cycles) in maintenance for 24 months.

[11] Additional visit to be performed within 30 days after last trial drug administration regardless of the radiological evaluations/follow-up visits calendar

[12] To be performed every 4 months for 2 years and aligned with radiological evaluations calendar. Between 2 and 5 years, visits are left to investigator discretion; However, three visits per year will be recommended. Overall survival will be captured at 5 years.

[13] Randomization should occur within 3 days prior to Cycle 2 Day 1.

[14] Imaging to be performed at screening, at C7D1 before the start of niraparib maintenance and then every 18 weeks during the 2 first years from randomization. After 2 first years, to be performed at investigator's discretion, 2 imaging per year recommended.

[15] Vital signs include weight, blood pressure, heart rate, temperature and height (at screening only).

[16] Type of visit during maintenance: protocol allows for patient in arm A to perform teleconsultation (TC). However, patient must be present on every 3 cycles.

[17] To be collected if patient is present on site.

[18] For laboratory assessment to be performed please refer to section 8.3. Laboratory assessment can be performed more frequently

at investigator's discretion.

[19] Hematology to be performed weekly during the first month of maintenance (W1 to W4 of maintenance).

[20] For maintenance therapy eligibility assessment, please refer to section **Erreur ! Source du renvoi introuvable.**

[21] For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to GSK. A copy of the hematologist's report of aspirate/biopsy findings including a classification according to WHO criteria and other sample testing results related to MDS/AML will be provided to the sponsor and to GSK.