SYNOPSIS

Title	**A MULTICENTER, OPEN-LABEL PHASE II TRIAL OF A NEW CUSTOMIZED DOSING (RATIONAL ADJUSTMENT OF DOSE TO REDUCE ADVERSE REACTIONS "RADAR" DOSING) OF NIRAPARIB AS MAINTENANCE THERAPY IN PLATINUM SENSITIVE OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL RECURRENT CANCER PATIENTS.**
EudraCT number	2018-003736-77
Study Acronym	NEWTON (NEW dosing mainTenance therapy Ovarian caNcer)
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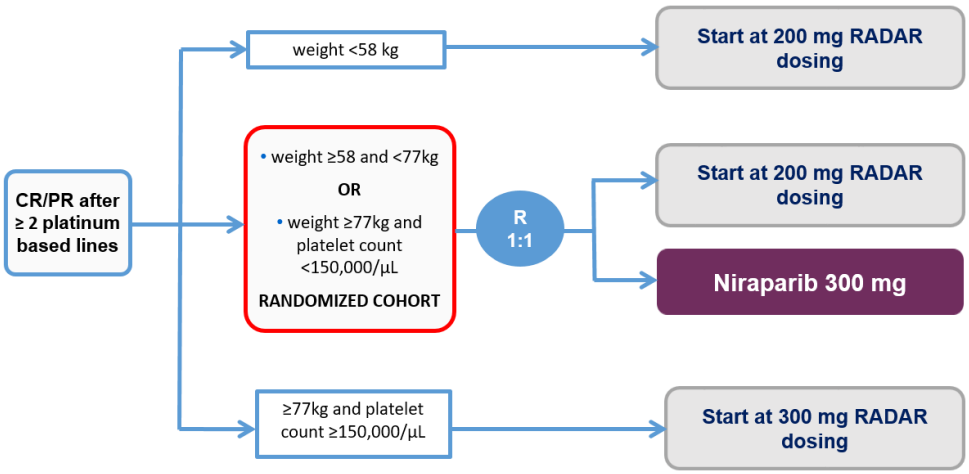
Experimental phase	II
Background and rationale	Maintenance therapies after a platinum based regimen are administered in ovarian cancer (OC) to improve the progression free survival and delay the platinum re-treatment. In the past several years the class of adenosine diphosphate [ADP]–ribose polymerase (PARP) inhibitors have been extensively studied in OC as maintenance therapy, showing promising clinical benefit especially in patients with platinum-sensitive recurrent disease. Preliminary antitumor activity of the new highly specific PARP1/2 inhibitor niraparib was firstly observed in a phase I dose-escalation study, which identified a 300 mg daily dose as recommended dose able to determine an objective clinical response with low frequency of high grade toxic effects. More recently, the efficacy and safety of niraparib as maintenance therapy after completion of platinum-based chemotherapy was evaluated in ENGOT-OV16/NOVA study, a randomized, double-blind, placebo-controlled phase 3 trial in patients with platinum-sensitive recurrent OC. Treatment with niraparib was demonstrated to significantly prolong the progression free survival regardless of germline BRCA1/2 mutational status and presence of Homologous Recombination Deficiencies (HRD), being worth approval by the American and European Regulatory Agencies. Despite clear efficacy, treatment dose of 300 mg daily gave rise to grade 3-4 thrombocytopenia, anemia, and neutropenia in 34%, 25% and 20%, respectively, of patients. Hematological abnormalities developed during the first three 28-day cycles and grade 3-

	4 thrombocytopenia mostly within the first two 28-day cycles. Such toxicities were manageable with drug suspension and dose reductions and did not appear to be cumulative, thus suggesting a margin for treatment schedule optimization and safety profile improvement. An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that baseline platelets had an impact on platelet nadir; lower baseline platelets (<180,000/µL) were associated with an increased frequency of thrombocytopenia grade ≥1 (76%) or grade ≥3 (45%) compared to patients with higher baseline platelet counts. The relevance of baseline body weight was assessed in further exploratory analyses of ENGOT-OV16/NOVA trial. For this analysis, the lowest weight quartile (patients with a body weight less than 58 kg at baseline) was compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While Treatment Emergent Adverse Events (TEAEs) occurred in most patients regardless of body weight, grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lowest body weight quartile (24%) compared to patients in the highest quartile (10%). The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of grade 3 or 4 thrombocytopenia and baseline body weight. The lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during cycle 1. In the first 30 days of treatment, a baseline body weight >77 kg was associated with a lower incidence of grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight <58 kg (43%). Based on this analysis, the Summary of Product Characteristics (SmPC) approved of niraparib was revised allowing the clinician to administer a reduced starting dose of 200 mg in patients who weigh less than 58 kg. Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥ grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg or baseline platelet count <150,000 µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg and a platelet count >150,000 µL. Furthermore, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 µL, and was only 206 mg for patients with body weight <77 kg or platelet count <150,000 µL. Thus, in this last subgroup, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. Based on these exploratory analyses a new dosing schedule called RADAR (**Rational Adjustment of Dose to reduce Adverse Reactions)** was developed. The RADAR dosing requires that 200 mg daily is administered for the first three 28-day cycles for patients who either weight less than 77 kg or have a baseline platelet count less than 150,000/µL.

	In these patients, dose can be escalated to 300 mg daily only if no hematological toxicities (defined as adverse event [AE] of any grade for platelets, or of grade ≥ 3 for neutrophils and hemoglobin) during the first three cycles occur. For patients with a body weight ≥ 77 kg and a platelet count ≥ 150,000/µL the starting dose is 300 mg. Although a toxicity reduction factor has already been incorporated in the SmPC that currently foresees the administration of 200 mg of niraparib as starting dose in patients with body weight < 58 kg, the aim of the present study will be to evaluate whether the adoption of the RADAR dosing strategy could further reduce treatment related toxicities improving the safety profile of niraparib, while preserving efficacy.
Study objectives *Primary*	The primary objectives of the study are: • to compare the safety profile of niraparib RADAR dosing in terms of occurrence of grade ≥ 3 thrombocytopenia in the first three cycles versus the SmPC approved dosing in patients who either have a baseline body weight ≥58 and <77kg, or have a baseline body weight ≥77kg and baseline platelet count <150,000/µL (restricted population); • to evaluate the improvement in the safety profile of niraparib RADAR dosing in terms of occurrence of grade ≥ 3 thrombocytopenia in the first three cycles based on the safety data from ENGOT-OV16/NOVA study.
Secondary	The secondary objectives of the study include: • to compare the safety profile of niraparib RADAR dosing in terms of occurrence of grade ≥ 3 thrombocytopenia in the first six cycles versus the SmPC approved dosing in patients who either have a baseline body weight ≥58 and <77kg, or have a baseline body weight ≥77kg and baseline platelet count <150,000/µL (restricted population); • to evaluate the improvement in the safety profile of niraparib RADAR dosing in terms of occurrence of grade ≥ 3 thrombocytopenia in the first six cycles based on the safety data from ENGOT-OV16/NOVA study. Further secondary objectives are: • Efficacy: o to compare the efficacy of niraparib RADAR dosing vs. the SmPC dosing (300 mg) (restricted population). o to evaluate the efficacy of niraparib RADAR dosing. • Safety: o to compare the general safety profile of niraparib RADAR dosing compared with the SmPC dosing (300 mg) (restricted population). o to evaluate the safety of niraparib RADAR. • Compliance: to evaluate patients adherence to the two treatment regimens of niraparib (RADAR and SmPC) under study in terms of average administered dose in the first 6 cycles. • Pharmacokinetic: to assess the minimum level of niraparib at the steady state, i.e. trough level concentration and the peak level at two hours after the daily dose Then the relation between the minimum level of niraparib at the steady state and

	the peak level with the patient's clinical characteristics, dose administered including average dose and toxicities registered during treatment will be evaluated.
Study design	This is a phase II study built up by **a randomized and a non-randomized part**. Randomized part: Patients who either have a baseline body weight ≥58 and <77kg, or have a baseline body weight ≥77kg and baseline platelet count <150,000/µL (named as restricted population) will be randomly assigned to receive RADAR dosing or the SmPC dosing. The rationale to perform the randomized comparison within this restricted population is that only in this population the starting doses are different between RADAR (200 mg daily) and SmPC (300 mg daily) regimens. For the rest of patients, both RADAR and SmPC treatment strategies have similar starting doses. Randomization ratio will be 1:1 and will be based on a minimization procedure accounting for the following factors: i. platinum sensitivity (6 to <12 months vs. ≥12 months); ii. use of bevacizumab in conjunction with the penultimate platinum based therapy; iii. best response (complete or partial) during the last platinum regimen. No-randomized part: Patients with weight <58 or ≥77kg and baseline platelet count ≥150,000/µL will be enrolled into the study but not randomized. The overall RADAR cohort will be composed of the patients assigned to RADAR dosing either through randomization or no-randomized enrollment. A capping procedure will be applied to the no-randomized population to have a final RADAR cohort matching the weight distribution of the NOVA population (i.e. approximately the lowest and highest weight quartile of 58 and 77 kg, respectively) in order to guarantee a correct indirect comparison. 
Number of centers	13 sites: 10 in Italy and 3 outside Italy (in Germany)
Number of patients	105 according to the sample size calculation.

Target population *Inclusion criteria*	1. 18 years of age or older, female, any race 2. Histologically diagnosed ovarian cancer, fallopian tube cancer or primary peritoneal cancer 3. High grade serous or high grade endometrioid (grade 2 or 3) histology or known to have BRCAmut (somatic or germline) 4. Has received at least 2 previous lines of platinum-containing therapy (not necessarily consecutive), and has disease that was considered platinum sensitive following the penultimate platinum line (more than 6-months period between penultimate platinum regimen and progression of disease) 5. Has responded to the last platinum line (PR or CR) 6. No more than 8 weeks have elapsed from completion of the last platinum regimen and the patient is still not progressing after response 7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 8. Adequate bone marrow, kidney and liver function, defined as follows: a. Absolute neutrophil count ≥ 1,500/µL b. Platelets ≥ 100,000/µL c. Hemoglobin ≥ 9 g/dL d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation e. Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN f. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN 9. Patient receiving corticosteroids may continue as long as their dose is stable for least 4 weeks prior to initiating protocol therapy. 10. Patient must have a negative urine or serum pregnancy test within 7 days prior to taking study treatment if childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment or use highly effective contraception throughout the study. Such methods include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner. Non-childbearing potential is defined as follows (by other than medical reasons): ≥45 years of age and has not had menses for >1 year; patients with amenorrhea for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation; Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical

	records, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. 11. Patient must agree to not breastfeed during the study and for 180 days after the last dose of study treatment. 12. Patient must be able to understand the study procedures and agree to participate in the study by providing written informed consent. 13. Patients must have normal blood pressure or adequately treated and controlled hypertension. (i.e. systolic BP ≤ 140 mmHg and diastolic BP ≤ 90 mmHg)
Exclusion criteria	1. Patient simultaneously enrolled in any interventional clinical trial 2. Invasive cancer other than ovarian cancer within 2 years (except basal or squamous cell carcinoma of the skin that has been definitely treated) 3. Patient with known, symptomatic brain or leptomeningeal metastases 4. Patient with immunocompromised status 5. Patient with known active hepatic disease 6. Prior treatment with a known PARP inhibitor 7. Patient who has had major surgery ≤ 3 weeks prior to initiating protocol therapy and participant must have recovered from any surgical effects. 8. Patient who has received investigational therapy ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is shorter, prior initiating protocol therapy. 9. Patient has had radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to day 1 of protocol therapy 10. Patient has had any radiation therapy within 1 week prior to day 1 of protocol therapy. 11. Patient with known hypersensitivity to niraparib components or excipients. 12. Patient has received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to initiating protocol therapy. 13. Patient has received colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 4 weeks prior initiating protocol therapy. 14. Patient has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment. 15. Patient with any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)

	16. Patient with a serious, uncontrolled medical disorder. Examples include, but are not limited to, nonmalignant systemic disease, active, uncontrolled infection, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent
Treatment	Patients who either have a baseline body weight ≥58 and <77kg, or have a baseline body weight ≥77kg and baseline platelet count <150,000/µL (restricted population), they will be randomized in a 1:1 ratio to the treatments as specified below: 1. Arm A - SmPC approved dosing: niraparib administered once daily at 300 mg continuously during a 28-day cycle 2. Arm B - RADAR dosing: niraparib administered at a starting dose of 200 mg once daily continuously for the first three 28-day cycles. Subsequent escalation will be allowed to 300 mg daily, if no hematological toxicity occurs (any grade for platelet, or grade ≥ 3 for neutrophils and hemoglobin). For patients who either have a baseline body weight <58 kg, or have a baseline body weight ≥77kg and baseline platelet count ≥150,000/µL, they will be enrolled in a non-randomized fashion in the RADAR dosing arm. Treatment will be continued until progression, unacceptable toxicity, patient or physician decision to discontinue or death.
Assessment schedule	All patients will undergo the following examinations: • Disease evaluation: computed tomography or magnetic resonance imaging to assess disease progression will be performed at baseline and subsequently according to clinical practice provided that a tumor assessment is done at 6 months after randomization/enrollment to permit the PFS-6 secondary endpoint analysis. CA-125 assessment will not be considered sufficient to state disease progression. • Safety: will be assessed by monitoring patients for adverse events, laboratory testing, measuring vital signs, and conducting physical examinations. Laboratory test, vital signs and physical examination will be performed on days 1 and 15 of the first cycle, and day 1 of each subsequent cycle. Blood pressure and heart rate will be monitored weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with niraparib. Blood count will be evaluated once a week (day 1, 8, 15, 21) for the first cycle and the cycle at which eventual dose escalation will be carried out (4th cycle). For all other cycles the blood count will be evaluated at day 1. • Pharmacokinetics: blood samples for pharmacokinetic analyses will be collected at the first, the second, and the third and at the cycle at which the possible dose escalation will be carried out (the 4th cycle). The samples will be collected on day 1 before the daily dose administration and 2 hours after the drug intake. In addition, only at cycle 1 and 4 a second sample will be collected on day 15, before the daily dose administration. Further samples for PK analyses will be collected on

	the first day of any cycle at which the dose of niraparib is reduced and on day 1 of the subsequent cycle.
Endpoints *Primary* *Secondary*	• **Safety** - Rate of patients experiencing a grade ≥3 thrombocytopenia during the first three cycles. - Rate of patients experiencing a grade ≥3 thrombocytopenia during the first six cycles - Maximum toxicity grade experienced by each patient, for each toxicity, according to NCI-CTCAE v. 4.03 - Patients experiencing grade 3-4 toxicities for each toxicity - Type, frequency and nature of SAEs - Patients with at least a SAE - Patients with at least a SADR - Patients with at least a SUSAR • **Efficacy** ○ PFS-6: PFS rate at 6 months, defined as the proportion of patients alive and free from progression at 6 months after randomization. ○ PFS, defined as the time from the date of treatment randomization to the date of first documentation of progression or death whichever occurs first. ○ OS at 24 months, defined as the rate of patients who are alive at 24 months from randomization • **Pharmacokinetics** ○ Trough level of niraparib concentration at steady state (Css) and peak level at 2 hours after dosing. • **Compliance** ○ Number of administered cycles ○ Frequency and reasons for drug discontinuation and treatment modification (suspension, dose reduction). ○ Dose intensity
Planned study period	The study length will be of 42 months: 18 months of accrual and 24 months of follow-up. The end of the study is planned 24 months after the last patient enrolled.
Statistical methods *Sample size*	In the NOVA trial, 34% of patients treated with niraparib experienced grade 3-4 thrombocytopenia, most of which occurred during the first 3 cycles.[1] This proportion is 35% in the NOVA patients treated with niraparib who either had a baseline body weight ≥58 and <77kg, or had a baseline body weight ≥77kg and baseline platelet count <150,000/µL. Within this restricted population (the population assigned to the randomized cohort in this trial), the SmPC starting dose is once daily at 300 mg, whereas the RADAR starting dose is once daily 200 mg. We assume that the SmPC arm will experience an incidence of grade 3-4 thrombocytopenia of 35% in the restricted population, the same as that of NOVA historical data. In the RADAR arm we assume that the incidence of grade 3-4 thrombocytopenia will be reduced to 15% (within the restricted population aforementioned, and also in all-comers). It is also planned that the population randomized to RADAR arm will accounts for 50% of the all-comers in the overall RADAR

cohort, similar to the patient population distribution observed in NOVA niraparib-treated patients (a capping procedure will be applied).

The sample size calculations were driven considering the two primary objectives:

1) the comparison of RADAR dosing vs. SmPC dosing in the randomized patients in terms of safety 2) the evaluation of RADAR dosing safety according to NOVA historical control data in the entire RADAR cohort.

Primary objectives	**rate of grade ≥3 thrombocytopenia**	**Alpha (1-sided)**	**Power**	**Sample size**	**Remark**
RADAR vs SmPC (restricted population)	15% vs 35%	0.14	0.80	33 vs 33 (1:1)	Sample size based on normal approximation
RADAR safety evaluation (entire RADAR cohort)	34% or more (p0): the new RADAR dosing is not sufficiently safer based on NOVA data; 15% or less (p1): the new RADAR dosing is considered interesting for its safety profile.	0.01	0.89	66	Sample size based on Fisher's exact test. The test is positive if out of 66, 13 or less RADAR patients experience grade ≥3 thrombocytopenia.

- **Restricted population**: patients who either had a baseline body weight ≥ 58 and < 77kg, or had a baseline body weight ≥ 77kg and baseline platelet count <150,000/μL.
- This study has two primary objectives. The study is positive if at least one of the tests is significant
- The study total type-1 error is 1-sided 0.15 (0.01+0.14)
- With 66 patients enrolled in the RADAR cohort, this study has 89% power to detect a rate of grade ≥ 3 thrombocytopenia of 15% with a higher confidence interval excluding the 34% at 1-sided 0.01 alpha level.
- Considering 5% drop out rate, we need to enroll in total 105 patients

	– 70 patients in RADAR with a minimum of 35 patients in the restricted population – 35 patients in SmPC in the restricted population • Multiplicity adjustment at the primary analysis: – If the comparison RADAR vs SmPC in the restricted population is statistically significant at the pre-specified alpha level, the test in the entire cohort will be carried out at the full alpha level of 1-sided 0.15 according to the graphical approach of Maurer and Bretz. The primary analysis will be conducted in the Per Protocol (PP) population. PP population is defined as all patients who received at least one dose of study drug according to the treatment assignment.