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Clinical trial

Rational adjustment of dose to reduce adverse reactions (RADAR) in patients with platinum-sensitive recurrent ovarian cancer: Results from the phase II NEWTON trial (ENGOT-ov49)

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ABSTRACT

Background: Retrospective analyses of niraparib trials showed that baseline platelets and weight were associated with occurrence of G ≥ 3 thrombocytopenia. A rational adjustment of dose to reduce adverse reactions (RADAR) strategy was never prospectively compared with standard dose.

Methods: NEWTON aimed to evaluate the safety of niraparib RADAR dosing strategy in pts with platinum-sensitive, high-grade serous and endometroid ovarian, fallopian tube, or primary peritoneal cancer, as well as in pts with ovarian cancer and a germline or somatic BRCA mutation, irrespective of histologic subtype. Pts with weight≥ 58 and < 77 kg, or ≥ 77 kg with platelet count < 150,000/μL were randomized to receive niraparib 200 mg (RADAR) or 300 mg (standard). Pts < 58 kg were assigned to 200 mg (RADAR), and pts ≥ 77 kg with baseline platelet count ≥ 150,000/μL were assigned to 300 mg (RADAR). For pts assigned to 200 mg, in the absence of thrombocytopenia, severe neutropenia or anemia within cycle 3, dose escalation to 300 mg was considered at cycle 4. The primary endpoint was G ≥ 3 thrombocytopenia within cycle 3.

Results: 48 pts were randomized to RADAR or standard dose (300 mg/day) and 34 pts were assigned to RADAR without randomization. A total of 58 pts was included in the entire RADAR cohort. In the randomized part, a lower G≥ 3 thrombocytopenia incidence was observed in the RADAR compared to standard arm (4.2%, vs 41.7%, corresponding to a difference of −37.5%, 72%CI −49.2; −25.8, Z-test p= 0.0044). In the RADAR cohort,

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6 pts out of 57 had G≥ 3 thrombocytopenia (10.5%, 70% CI: 5.2–18.6;). Median PFS was 10.3 and 11.7 months in the randomized RADAR and 300 mg arms. The median PFS in the entire RADAR cohort was 10.0 months. *Conclusions:* Niraparib RADAR dosing is associated with a lower incidence of severe thrombocytopenia. Clinicaltrials.gov number: NCT03891576

1. Introduction

Ovarian cancer (OC) is one of the leading causes of death from gynecological cancer worldwide [1,2]. Approximately 70% of patients with advanced OC, though initially responsive to platinum chemotherapy, relapse and subsequent treatments are less effective. Optimal debulking surgery and platinum sensitivity correlate with better outcomes [3].

The NOVA/ENGOT-OV16 trial showed a PFS benefit with niraparib maintenance among patients with platinum-sensitive OC after partial/complete response to the last platinum line. This benefit was consistent regardless of germline BRCA 1/2 mutations (gBRCAm) or homologous recombination deficiencies (HRD) [4,5]. In this setting, also olaparib and rucaparib yielded a PFS benefit among patients with BRCAm (SOLO2/ENGOT-Ov21 trial) or regardless of biomarker status (ARIEL3 trial), respectively [6,7].

Additionally, a clinical benefit with PARPi maintenance - mainly driven by PFS improvement - was demonstrated in first-line setting advanced OC, both with olaparib in BRCAm (SOLO1 trial) and niraparib and rucaparib regardless of BRCA and HRD status (PRIMA, and ATHENA-MONO trials) [8–10].

EMA approved olaparib, niraparib and rucaparib as maintenance therapy in both first-line and recurrent settings, in BRCAm patients for olaparib and regardless of mutational status for niraparib and rucaparib.

Despite an acceptable tolerance profile, hematological toxicities (including anemia, thrombocytopenia, and neutropenia) were very common during the PARPi treatment.

In particular, in the NOVA trial, niraparib led to a higher incidence of grade 3–4 treatment-emergent adverse events (TEAEs) compared to placebo: 74.1% vs 22.9%. Due to TEAEs, many patients underwent dose interruption (68.9% vs 5%), dose reduction (66.5% vs 14.5%) and discontinuation (14.7% vs 2.2%). Most of the TEAEs were hematological with thrombocytopenia being the most frequent (61.3% vs 5.6% any grade; 33.8% vs 0.6% grade ≥3), followed by anemia and neutropenia. Notably, thrombocytopenia was the main cause of dose reduction, and it was most prevalent within the first 3 cycle of treatment. Indeed, the majority of patients received a lower dose than the 300 mg/day established by the phase I trial, thus improving safety beyond cycle 3 [11]. Patients with body weight < 58 kg had a particularly high incidence of TEAEs, and this led to the Summary of Product Characteristics (SmPC) being updated, indicating that 200 mg/day is the best dose for these patients. However, a retrospective analysis using the NOVA dataset showed that also patients with a body weight between ≥ 58 and < 77 kg or ≥ 77 kg and baseline platelet count < 150,000/μL experienced a significant rate of hematologic-TEAEs with the planned standard 300 mg/day dose, ultimately resulting in an average niraparib dosing levels of 207 mg daily (due to dose interruptions and reductions) [12,13].

In the PRIMA trial, an amendment introduced an individualized starting dose (200 mg/day for patients with body weight < 77 kg or platelet count < 150,000/μL, and 300 mg/day for patients with body weight ≥ 77 kg and platelet count ≥ 150,000/μL), which resulted in a better tolerance [14].

Therefore, the NEWTON study aimed to prospectively assess whether a new customized dosing strategy based on body weight and baseline platelet count, called RADAR (Rational Adjustment of Dose to reduce Adverse Reactions), would reduce thrombocytopenia incidence; pharmacokinetic samples were also collected as a sub-study to further explore drug exposure–toxicity relationships.

2. Methods

2.1. Participants/patients

NEWTON enrolled patients with histologically diagnosed high-grade serous or high-grade endometrioid ovarian, fallopian tube, or primary peritoneal cancer, as well as patients with ovarian, fallopian tube, or primary peritoneal cancer and a known somatic or germline BRCA mutation, irrespective of histologic subtype. Patients must have received at least 2 previous lines of platinum therapy (not necessarily consecutive) with a platinum-sensitive disease, referring to the penultimate platinum regimen (>6 months between treatment end and progression) and a partial or complete response to the last platinum line without any sign of progression within 8 weeks from therapy completion. No previous PARPi treatment was allowed. Patients had to be aged ≥ 18 years, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 1 and normal organ and bone marrow function. Full eligibility criteria are provided in the protocol (appendix S2). All patients provided written informed consent.

The protocol and subsequent amendments were approved by Competent Authorities and applicable ethics committees of the countries involved. ClinicalTrials.gov number: NCT03891576; EudraCT 2018–003736–77.

2.2. Study design and treatment

This multicenter, open-label, phase II trial aimed to assess the safety benefit of the RADAR dosing strategy.

The proposed RADAR dosing strategy was as follows:

- Patients weighing < 77 kg: starting dose 200 mg/day
- Patients weighing ≥ 77 kg with baseline platelet count < 150,000/μL: starting dose 200 mg/day
- For all patients starting at 200 mg/day, dose escalation to 300 mg/day was permitted at cycle 4 if no hematologic TEAEs had occurred (defined as any-grade thrombocytopenia, grade ≥3 neutropenia, or anemia according to CTCAE v4.03).
- Patients weighing ≥ 77 kg with platelet count ≥ 150,000/μL: starting dose 300 mg/day

The cycle length in all groups was 28 days (+/- 3 days).

Eligible patients with either a baseline body weight ≥ 58 and < 77 kg or a baseline body weight ≥ 77 kg and a platelet count < 150,000/μL were randomized with a 1:1 ratio to receive either niraparib at a standard dose of 300 mg/day (according to SmPC – standard arm) or niraparib at the initial dose of 200 mg daily (RADAR arm). Randomization was concealed using an interactive web-response system and minimization procedure, stratified by platinum sensitivity, use of bevacizumab with the penultimate platinum-based regimen and response during the last platinum-based regimen.

Eligible patients with body weight < 58 kg were assigned - without randomization - to receive niraparib starting dose of 200 mg/day according to the RADAR dosing; patients weighing ≥ 77 kg and with a baseline platelet count ≥ 150,000/μL were assigned to receive niraparib 300 mg/day according to the RADAR dosing.

The entire RADAR cohort consisted of patients enrolled in the randomized RADAR dosing arm together with patients who were assigned to RADAR non-randomly. In case of non-hematologic TEAEs of grade ≥ 3, niraparib treatment was interrupted until resolution to grade ≤ 1 or

baseline, with mandatory dose reductions (from 300 mg/day to 200 mg/day and 200 mg/day to 100 mg/day) upon resumption. For hematologic TEAEs, interruption was required if neutrophils $< 1000/\mu L$, hemoglobin ≤ 8 g/dL, or platelets $< 100{,}000/\mu L$. Treatment resumed at the same or reduced dose once neutrophils were $\geq 1500/\mu L$, hemoglobin ≥ 9 g/dL, and platelets $\geq 100{,}000/\mu L$; dose reduction was mandatory for any episode in which platelets had dropped below $75{,}000/\mu L$, whereas in other situations, dose adjustments were left to the investigator's discretion. Recurrent TEAEs of similar or greater severity required further interruption and dose reduction. Treatment was permanently discontinued if toxicity persisted for > 28 days, the maximum dose reductions had already been reached, or in cases of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), disease progression, or patient or physician decision to discontinue.

2.3. Assessments

Tumor assessments were performed by computed tomography or magnetic resonance imaging at baseline, at 6 months from registration/randomization and subsequently according to clinical practice timing until disease progression. Assessments were evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST criteria) version 1.1.

Blood count was evaluated weekly (day 1, 8, 15, 21) for cycle 1, during the cycle of the dose escalation (i.e., fourth cycle) and in case of dose interruption or reduction due to hematologic toxicity until AE resolution and for the 4 subsequent weeks at the new dosage.

2.4. Pharmacokinetics study

Blood samples for pharmacokinetics (PK) analysis were routinely collected pre-dose and 2 h post-dose on day 1 of the first 3 cycles and pre-dose on day 15 of cycle 1. Additional sampling was performed in specific cases: if dose escalation occurred during cycle 4, samples were collected pre- and post-dose on day 1, and pre-dose on day 15; in case of dose reduction, pre-dose samples were collected on day 1 of the cycle in which the dose was reduced, and again on day 1 of the subsequent cycle.

2.5. Outcomes and endpoints

Primary and secondary endpoints were evaluated separately for the randomized cohort, analyzed according to randomization arm, and the entire cohort of patients assigned to receive RADAR dosing (randomized or non-randomized).

The primary endpoint was the rate of patients experiencing grade ≥ 3 thrombocytopenia during the first 3 cycles of niraparib.

Secondary safety endpoints included the rate of patients experiencing grade ≥ 3 thrombocytopenia during the first 6 cycles and the safety profile, by assessing the worst grade experienced by each patient for each type of adverse event reported.

Secondary efficacy endpoints included PFS, PFS rate at 6 months (PFS-6), overall survival (OS), and OS rate at 24 months (OS-24). The PFS was defined from registration/randomization to progression or death, whichever occurred first. The OS was defined from the treatment registration/randomization to death.

Secondary endpoints included treatment compliance, in terms of treatment duration, number of cycles, frequency and reason for drug discontinuation, and dose intensity (defined as the administered dose in mg per time unit – i.e. day).

PK parameters were described, specifically niraparib concentrations at trough (before dosing) and at peak (2 h after the daily dose was taken).

2.6. Statistical methods

The rate of patients experiencing grade ≥ 3 thrombocytopenia during the first 3 cycles of niraparib reported in the NOVA trial was considered as the historical reference. The sample size was calculated for both the comparison of the primary endpoint between the RADAR arm and the control arm (standard 300 mg dose) in the randomized cohort, and the evaluation of the primary endpoint in the entire RADAR cohort. It was also planned that the population randomized to RADAR arm would account for 50% of the entire RADAR cohort. This mirrored the patient population distribution observed in the NOVA trial; therefore, a capping procedure was applied.

2.6.1. Sample size of randomized cohort

To detect a reduction in the rate of grade ≥ 3 thrombocytopenia in the randomized cohort from 35% to 15% in favor of RADAR dosing (one-sided alpha 14%, 80% power), 66 patients were required (33 pts in the RADAR arm and 33 pts in the 300 mg/day arm).

2.6.2. Sample size of entire RADAR cohort

Assuming that a primary endpoint rate $\geq 34\%$ in the entire RADAR cohort would not be clinically meaningful, whereas a rate $\leq 15\%$ would be considered safe, a sample size of 66 patients assigned to RADAR dosing (randomized or not) ensured a one-sided alpha error of 1% and 89% power.

If the randomized cohort showed a statistically significant result on the primary endpoint, the test in the entire RADAR cohort could be performed with a one-sided alpha of 15%, according to the graphical approach described by Maurer and Bretz [15].

2.6.3. ***Statistical analyses***

The primary endpoint rates were reported as the absolute and relative frequencies. Confidence intervals (CIs) were calculated using the exact binomial method. In the randomized cohort, Fisher's exact test was used to compare absolutefrequences between arms; the difference of the thrombocytopenia proportions was tested by means of Z-test.

The PFS, PFS-6, OS and OS-24 were described with the Kaplan-Meier (KM) method. The log-rank test and Cox proportional hazards model were used to assess the differences between arms in terms of PFS and OS. Results were presented as hazard ratios (HRs) and 95% CIs.

The correlation between the primary endpoint and specific PK parameters (i.e., peak plasma concentration) was evaluated using a multivariable logistic mixed model for repeated measures. Additionally, the association between the PK parameters (trough level and peak level) and clinical characteristics of patients were assessed using multivariable linear mixed models for repeated measures.

2.7. Trial oversight

The trial adhered to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws. The trial was designed and sponsored by the Mario Negri Institute on behalf of the Mario Negri Gynecologic Oncology (MaNGO) group, and it was conducted in collaboration with the North Eastern German Society of Gynecological Oncology (NOGGO) group. The sponsor was responsible for overseeing data collection, analysis, and interpretation.

Authors had full access to data, wrote and approved the manuscript, attested to the accuracy and completeness of data, confirmed adherence to the protocol, and made the final decision to submit the manuscript for publication. GlaxoSmithKline LLC. supported the trial but had no access to the data and did not contribute to the interpretation of the results or the writing of this article.

3. Results

3.1. Patients

The study was discontinued before reaching the target sample size because of decreased patient enrollment over time. Between November

2019 and January 2024, 92 patients were screened: 10 were screening failures and 82 were included in the NEWTON study. Out of these, 34 were assigned to the non-randomized arms (17 at 200 mg/day and 17 at 300 mg/day), while 48 were randomized to either 200 mg/day or 300 mg/day (24 patients per arm), for a total of 58 patients included in the entire RADAR cohort. One patient assigned to non-randomized RADAR 300 mg/day group had a wild-type clear cell histotype at screening, and she never received any study treatment; therefore, she was excluded from the primary endpoint and safety analyses. The study flowchart is depicted in Figure 1. Table 1 shows the demographic and clinical characteristics at screening and baseline of the 48 randomized patients and the 57 patients of the entire RADAR cohort included in the primary analysis (Table S1 shows the same characteristics according to all arms).

In the entire RADAR cohort, 55 (96.5%) patients had an ECOG PS equal to 0, the median age was 61.0 years (Q1-Q3: 56.0–69.0), the median weight was 68.0 kg (first quartile [Q1]-third quartile [Q3]: 56.0–78.3); 19 patients (33.9%) were mBRCA. In most of the mBRCA patients, mutations were germline (14 patients; 73.7%). Furthermore, 46 (80.7%) patients had a platinum-free interval $\geq$ 12 months at the penultimate platinum-based therapy, 34 (59.6%) received bevacizumab at the penultimate platinum-based line. Thirty-one (54.4%) and 26 (45.6%) patients had a partial or complete response to the last platinum line.

3.2. Treatment exposure

In the randomized arms, all patients received the study treatment (n = 48) with a median duration of treatment of 11.2 months (Q1-Q3: 4.0–17.6) in the RADAR 200 mg/day arm and 9.2 months (Q1-Q3: 5.7–22.9) in the standard 300 mg/day arm. Sixteen (33.3%) patients were still on treatment at study closure; out of 32 no longer under study treatment, 13 (92.9%) patients in the RADAR 200 mg/day arm and 14 (77.8%) in the standard 300 mg/day arm discontinued the treatment for disease progression, and only 1 (7.1%) patient discontinued for adverse event in the RADAR 200 mg/day arm (Table 2 and Table S2).

Fifty-seven patients in the entire RADAR cohort received the study treatment with a median number of cycles of 11.0 (Q1-Q3: 6.0–18.0); 14 (24.6%) patients were still under treatment at study closure. Of the 43 patients no longer under study treatment, 37 (86.0%) discontinued due to disease progression, while 3 (7.0%) discontinued the treatment due to adverse events (Table 2). Dose intensity values are reported in Table 2 and Table S2.

3.3. Thrombocytopenia

During the first 3 cycles, 1 (4.2%) and 10 (41.7%) patients experienced a grade $\geq$ 3 thrombocytopenia in the randomized RADAR 200 mg/day and in the randomized standard 300 mg/day arm, respectively, corresponding to a difference of −37.5% (72%CI −49.2; −25.8, Z-test p = 0.0044).

Within the entire RADAR cohort, 6 patients experienced grade $\geq$ 3 thrombocytopenia during the first 3 cycles (10.5%; 70% CI: 5.2–18.6; 95% CI: 3.4–23.2). Since the upper limit of the 70% confidence interval—predefined based on the study sample size—was below the historical reference incidence rate of 35% (and the upper limit of the 95% CI was also below 35%), the trial outcome was considered statistically positive.

Two patients (8.3%, 95% CI 1.0–27.0) in the randomized RADAR 200 mg/day arm and 10 patients (41.7%, 95% CI: 21.9–61.4, p = 0.0173) in the randomized standard 300 mg/day arm experienced a grade $\geq$ 3 thrombocytopenia during the first 6 cycles. In the entire RADAR cohort, 7 patients experienced a grade $\geq$ 3 thrombocytopenia during the first 6 cycles (12.3%, 95% CI: 5.1–23.7) (Table S3).

Data on thrombocytopenia occurrence in the first 3 and 6 cycles according to the assigned dosing group are reported in Table S3.

3.4. Pharmacokinetics

Table S4 reports the niraparib concentrations at different time points across treatment dosing groups. According to the multivariable logistic mixed model, no significant correlation between peak levels and grade $\geq$ 3 thrombocytopenia was found during the first three cycles (Table S5).

The boxplots displaying the trough and peak levels of niraparib according to treatment dosing group in the first three cycles are shown in Fig. 2.

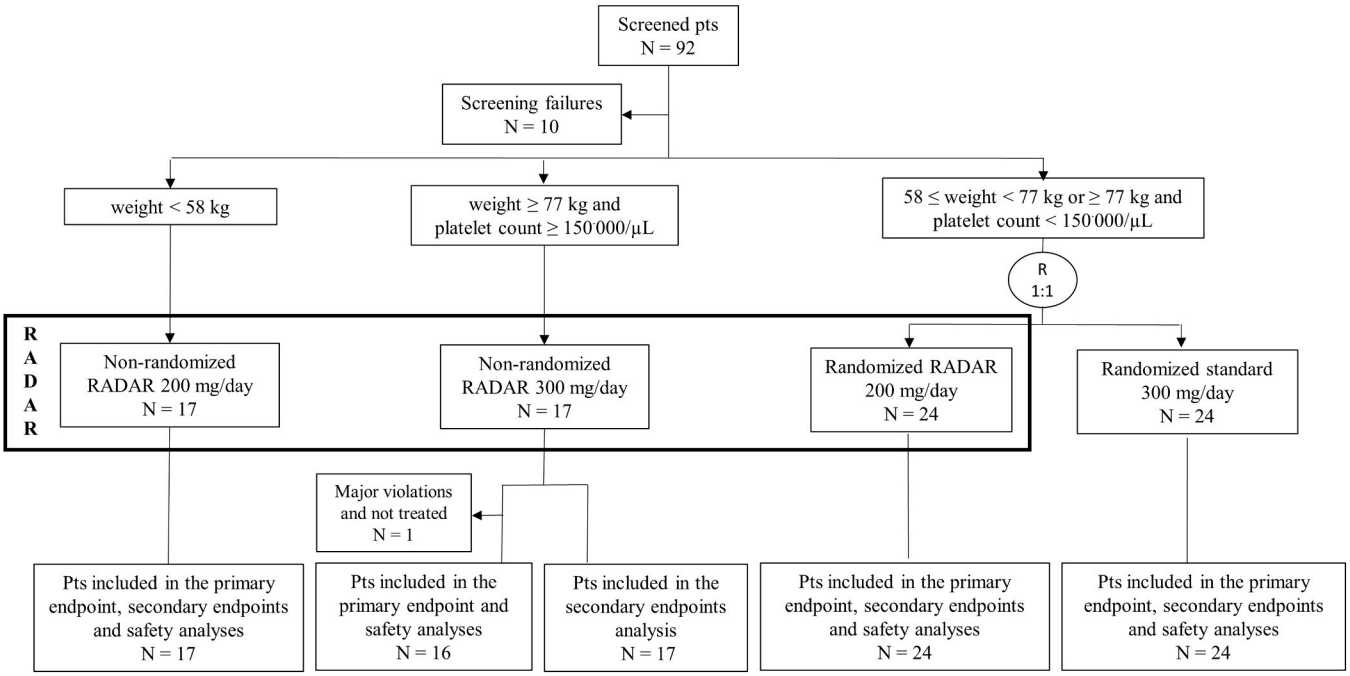

Fig. 1. Study flowchart. **Legend**: N: number of patients; R: randomized; NR: Not randomized.

Table 1
Demographic and baseline characteristics.

	Rand. RADAR 200 mgN= 24	Rand. 300 mgN= 24	Entire RADAR cohortN= 57
Platelet count (1000/μL)			
Median (Q1 - Q3)	219.5 (165.0–280.5)	211.5 (166.0–255.5)	192.0 (166.0–260.0)
Age			
Median (Q1 - Q3)	62.5 (56.0–68.5)	63.5 (58.5–70.5)	61.0 (56.0–69.0)
ECOG PS - n (%)			
0	23 (95.8)	22 (91.7)	55 (96.5)
1	1 (4.2)	2 (8.3)	2 (3.5)
Weight (Kg)			
Median (Q1 - Q3)	68.0 (63.5–72.0)	65.0 (62.0–71.0)	68.0 (56.0–78.3)
Height (cm)			
Median (Q1 - Q3)	165.0 (156.0–167.0)	160.0 (156.5–163.5)	160.0 (154.5–166.0)
Missing	1	0	1
Race - n (%)			
White	24 (100.0)	24 (100.0)	57 (100.0)
BRCA mutated - n (%)			
No	17 (70.8)	16 (66.7)	33 (58.9)
Yes	5 (20.8)	7 (29.2)	19 (33.9)
VUS	2 (8.3)	1 (4.2)	4 (7.1)
Missing	0	0	1
Type of test for BRCA - n (%)			
Germline	11 (50.0)	13 (56.5)	32 (59.3)
Somatic	11 (50.0)	10 (43.5)	22 (40.7)
Missing	2	1	3
F.I.G.O. stage - n (%)			
I	1 (4.2)	0 (0.0)	4 (7.0)
II	0 (0.0)	0 (0.0)	1 (1.8)
III	16 (66.7)	19 (79.2)	ho37 (64.9)
IV	6 (25.0)	5 (20.8)	12 (21.1)
Unknown	1 (4.2)	0 (0.0)	3 (5.3)
Histological type - n (%)			
Serous	24 (100.0)	23 (95.8)	56 (98.2)
Endometrioid	0 (0.0)	1 (4.2)	1 (1.8)
Number of previous chemotherapy lines - n (%)			
2	18 (75.0)	17 (70.8)	44 (77.2)
3	5 (20.8)	5 (20.8)	10 (17.5)
4	1 (4.2)	1 (4.2)	3 (5.3)
7	0 (0.0)	1 (4.2)	0 (0.0)
Platinum Sensitivity - n (%)			
[6−12) months	3 (12.5)	2 (8.3)	11 (19.3)
≥ 12 months	21 (87.5)	22 (91.7)	46 (80.7)
Use of bevacizumab in conjunction with penultimate platinum based therapy - n (%)			
No	9 (37.5)	9 (37.5)	23 (40.4)
Yes	15 (62.5)	15 (62.5)	34 (59.6)
Best response during last regimen - n (%)			
CR	11 (45.8)	12 (50.0)	26 (45.6)
PR	13 (54.2)	12 (50.0)	31 (54.4)

Legend: N: Number of subjects. Q1 - Q3: First – third quartile. VUS: Variant of Uncertain Significance.
Note. The entire RADAR cohort includes the randomized RADAR 200 mg arm and both non-randomized arms (200 mg and 300 mg).

From the multivariable linear mixed models, statistically significant correlations between serum creatinine (β[10 mg/dL difference] 81.56, 95% CI 14.22–148.89, p = 0.0182) and weight (β[10 kg difference] −39.69, 95% CI −78.14 to −1.25, p = 0.0432) with trough levels were detected during the first three cycles (Table S6). No significant correlations were detected between peak levels and dose or other clinical characteristics during the first three cycles (Table S7).

Table 2
Treatment description.

	Rand. RADAR 200 mgN= 24	Rand. 300 mgN= 24	Entire RADAR cohort N = 57
Patients who received treatment - n (%)	24 (100.0)	24 (100.0)	57 (100.0)
Treatment duration (months)			
Median (Q1 - Q3)	11.2 (4.0–17.6)	9.2 (5.7–22.9)	9.9 (6.0–17.0)
Number of cycles			
Median (Q1 - Q3)	11.5 (4.5–18.5)	10.0 (6.0–24.5)	11.0 (6.0–18.0)
Niraparib dose escalation to 300 mg - n (%)	4 (16.7)	0 (0.0)	5 (8.8)
Niraparib dose reduction to 200 mg - n (%)	3 (12.5)	19 (79.2)	18 (31.6)
Niraparib dose reduction to 100 mg - n (%)	9 (37.5)	7 (29.2)	19 (33.3)
Niraparib dose intensity (mg/day)			
Median (Q1 - Q3)	188.3 (110.9–195.7)	187.9 (141.9–231.5)	187.4 (124.5–197.9)
Missing	0	0	1
Treatment discontinued - n (%)	14 (58.3)	18 (75.0)	43 (75.4)
Reasons for discontinuation - n (%)			
Disease Progression	13 (92.9)	14 (77.8)	37 (86.0)
Adverse Event	1 (7.1)	0 (0.0)	3 (7.0)
Deterioration of clinical conditions or clinical decision	0 (0.0)	1 (5.6)	2 (4.7)
Patient refusal	0 (0.0)	2 (11.1)	0 (0.0)
Other primary tumor occurrence	0 (0.0)	0 (0.0)	1 (2.3)
Investigator decision	0 (0.0)	1 (5.6)	0 (0.0)
Still under treatment at study closure - n (%)	10 (41.7)	6 (25.0)	14 (24.6)

Legend: N: Number of subjects; Q1 - Q3: First - third quartile
Note. The entire RADAR cohort includes the randomized RADAR 200 mg arm and both non-randomized arms (200 mg and 300 mg).

3.5. Secondary endpoints

The median follow-up for the randomized cohort was 28.1 months (Q1-Q3: 13.1–43.0).

Overall, 32 (66.7%) patients had disease progression or died. A median PFS of 10.3 months (95% CI: 4.4-not reached) and 11.7 months (95% CI: 6.2–26.1) were observed in the randomized RADAR 200 mg/day arm and the randomized standard 300 mg/day arm, respectively. No significant PFS differences between the randomized arms were detected (log-rank p = 0.9339).

The PFS-6 was 70.8% (95% CI: 48.4–84.9) and 78.0% (95% CI: 55.0–90.2) in the randomized RADAR 200 mg/day and randomized standard 300 mg/day arms, respectively.

The univariable and multivariable Cox models confirmed no significant impact of the treatment arm on the PFS (Table S8).

The median follow-up for the entire RADAR cohort was 34.9 months (Q1-Q3: 19.0–42.1). A median PFS of 10.0 months (95% CI: 8.0–13.7) was observed, with 42 (72.4%) patients who either had disease progression or died. The PFS-6 was 75.4% (95% CI: 62.1–84.7).

The KM survival curves for PFS in the randomized and the entire RADAR cohorts are illustrated in Fig. 3, panels A and B, respectively.

In the randomized cohort, 13 (27.1%) patients died. A median OS of 37.9 months (95% CI: 24.9-not reached) and 36.4 months (95% CI: 23.9-not reached) were observed in the randomized RADAR 200 mg/day arm and the randomized standard 300 mg/day arm, respectively (Fig. 4A). No statistically significant differences between the randomized arms in

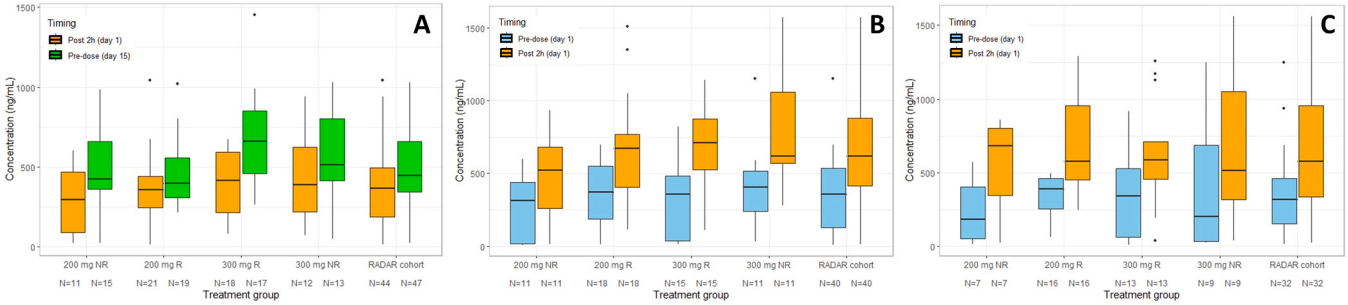

Fig. 2. (A) Boxplot for the peak (post 2 h) niraparib concentration at day 1 of cycle 1 and the trough (pre-dose) niraparib concentration at day 15 of cycle 1 according to treatment group. (B) Boxplot for the trough and peak niraparib concentrations at day 1 of cycle 2 according to treatment group. (C) Boxplot for the trough and peak niraparib concentrations at day 1 of cycle 3 according to treatment group. The boxplots show the median as the horizontal line, the lower and upper edges of the box as the 1st and 3rd quartiles and the whiskers as the vertical lines extending to the smallest and largest values within 1.5*IQR (interquartile range). Values that fall above or below are considered outliers and are displayed as dots. **Legend:** N: number of patients; R: randomized; NR: Not randomized. **Note.** The RADAR cohort includes the randomized 200 mg arm and both non-randomized arms (200 mg and 300 mg).

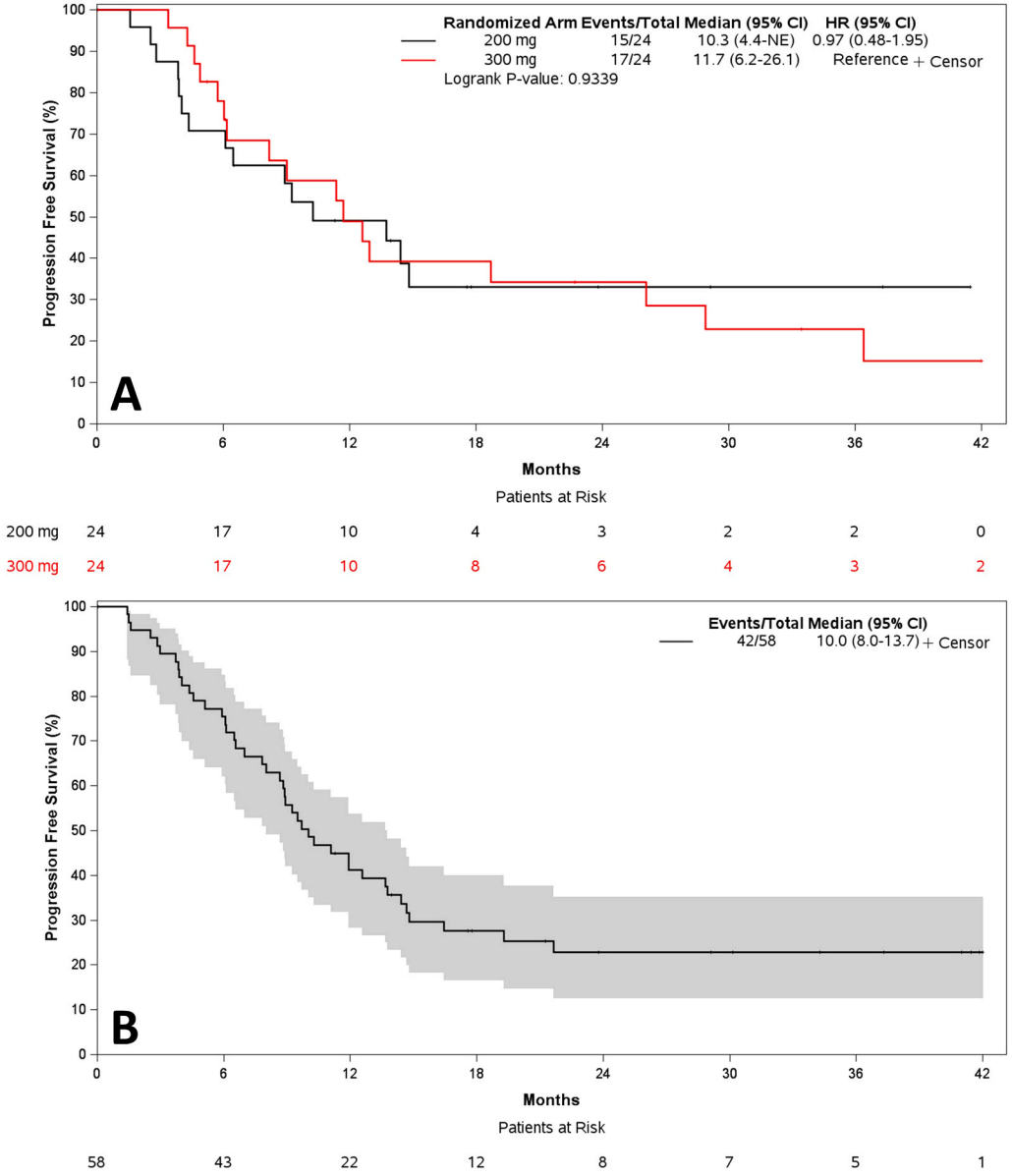

Fig. 3. (A) Kaplan-Meier curves for progression free survival in the randomized cohort according to treatment arm. (B) Kaplan-Meier curve for progression free survival in the entire RADAR cohort. The grey area represents the 95% confidence band of the curve. **Legend:** NE: Not estimated. CI: confidence interval. **Note.** The RADAR cohort includes the randomized 200 mg arm and both non-randomized arms (200 mg and 300 mg).

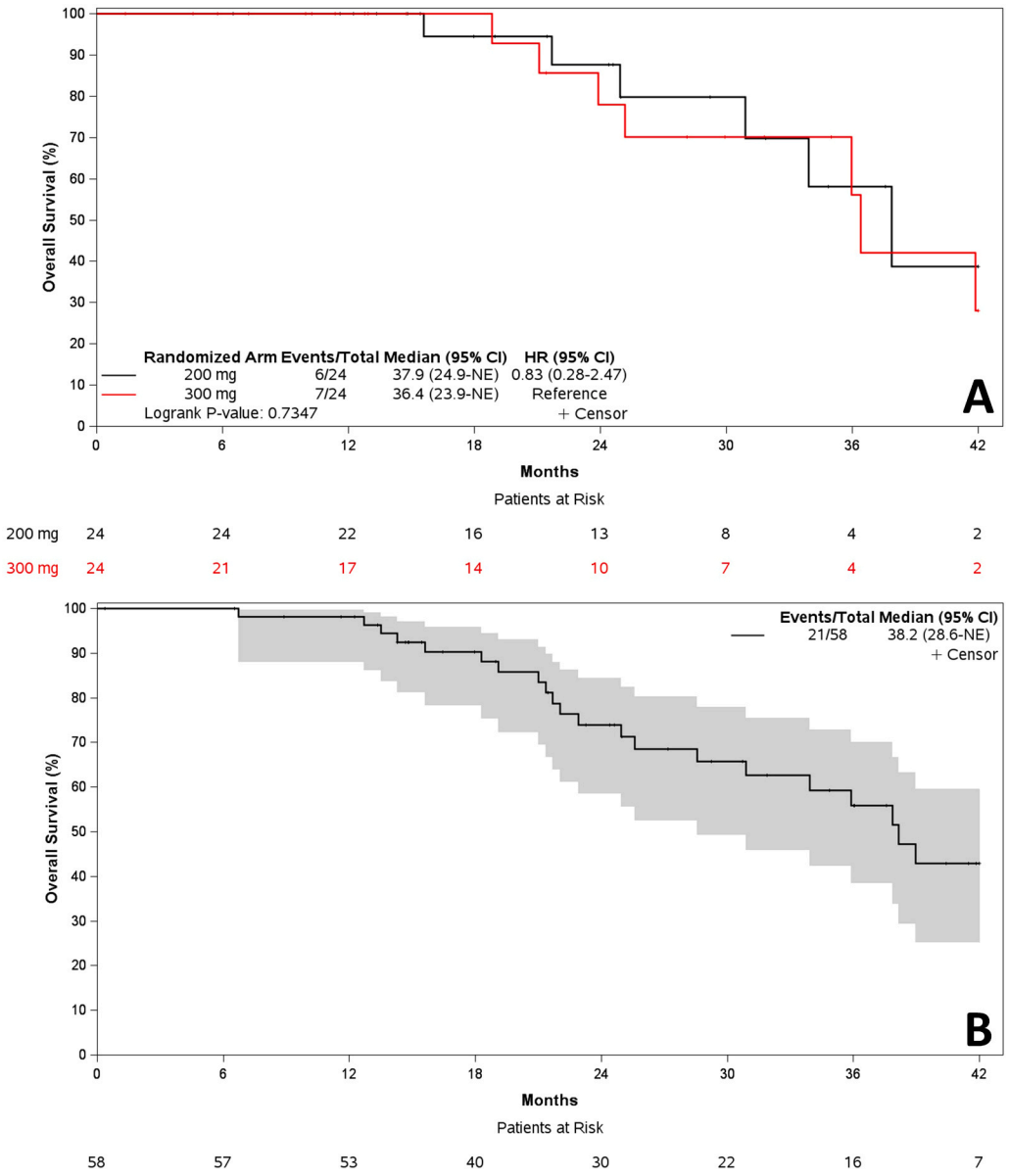

Fig. 4. (A) Kaplan-Meier curves for overall survival in the randomized cohort according to treatment arm. (B) Kaplan-Meier curve for overall survival in the entire RADAR cohort. The grey area represents the 95% confidence band of the curve. **Legend:** NE: Not estimated. CI: confidence interval. **Note.** The RADAR cohort includes the randomized 200 mg arm and both non-randomized arms (200 mg and 300 mg).

terms of OS were detected (p = 0.7347).

No significant impact of the treatment arm on the OS emerged from both the univariable and multivariable Cox models (Table S9).

The OS-24 was 87.7% (95% CI: 58.8–96.8) and 77.9% (95% CI: 45.9–92.3) in the randomized RADAR 200 mg/day arm and the randomized standard 300 mg/day arm, respectively.

Within the entire RADAR cohort, the median OS was 38.2 months (95% CI: 28.6-not reached), with 21 (36.2%) patients who died. The OS-24 was 74.0% (95% CI: 58.5–84.4).

The KM survival curves for OS in the randomized and the entire RADAR cohorts are illustrated in Figs. 4A and 4B, respectively.

3.6. Safety

A total of 579 TEAEs occurred in 56 of 57 patients (98.8%) who received niraparib of the entire RADAR cohort.

Treatment-emergent hematologic events of any grade that occurred in at least 10% of patients of the RADAR cohort, included thrombocytopenia (57.9%), anemia (50.9%), and neutropenia (21.1%). In the randomized arms, 45.8% of patients in the RADAR 200 mg/day arm and 66.7% of patients in the standard 300 mg/day arm experienced thrombocytopenia of any grade. Five cases of thrombocytopenia led to patient hospitalization (one in each randomized arm and 3 in the non-randomized RADAR arms). Other TEAEs accounting for more than 10% were: abdominal pain (10.5%), constipation (17.5%), nausea (36.8%), vomiting (17.5%), fatigue (40.4%), COVID-19 (15.8%), blood creatinine increased (24.6%), arthralgia (12.3%) and hypertension (28.1%) (Table 3 and Table S10).

Looking at dose reductions for adverse events in the RADAR cohort, 34 patients (59.6%) had niraparib reductions due to adverse events; the most common adverse events were thrombocytopenia (14 patients; 41.2%) and anemia (8 patients; 23.5%) (Table S5). In the randomized cohort, 12 (50.0%) patients in the RADAR 200 mg/day arm and 20 (83.3%) patients in the standard 300 mg/day arm reduced the niraparib dose due to adverse event with the most frequent event being thrombocytopenia (6 patients in the randomized RADAR 200 mg arm and 8 in

Table 3
Adverse events of any grade that occurred in at least 10% of patients and any adverse events of grade 4–5.

	Rand. RADAR 200 mgN= 24			Rand. 300 mgN= 24			Entire RADAR cohortN= 57		
	G1-G2n (%)	G3-G4n (%)	G5n (%)	G1-G2n (%)	G3-G4n (%)	G5n (%)	G1-G2n (%)	G3-G4n (%)	G5n (%)
Blood and lymphatic system disorders									
Anaemia	7 (29.2)	3 (12.5)	0 (0.0)	6 (25.0)	5 (20.8)	0 (0.0)	18 (31.6)	11 (19.3)	0 (0.0)
Neutropenia	3 (12.5)	3 (12.5)	0 (0.0)	4 (16.7)	3 (12.5)	0 (0.0)	9 (15.8)	3 (5.3)	0 (0.0)
Thrombocytopenia	9 (37.5)	2 (8.3)	0 (0.0)	6 (25.0)	10 (41.7)	0 (0.0)	25 (43.9)	8 (14.0)	0 (0.0)
Gastrointestinal disorders									
Abdominal pain	3 (12.5)	0 (0.0)	0 (0.0)	4 (16.7)	0 (0.0)	0 (0.0)	6 (10.5)	0 (0.0)	0 (0.0)
Constipation	4 (16.7)	0 (0.0)	0 (0.0)	5 (20.8)	0 (0.0)	0 (0.0)	10 (17.5)	0 (0.0)	0 (0.0)
Nausea	9 (37.5)	0 (0.0)	0 (0.0)	13 (54.2)	0 (0.0)	0 (0.0)	21 (36.8)	0 (0.0)	0 (0.0)
Vomiting	3 (12.5)	1 (4.2)	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	9 (15.8)	1 (1.8)	0 (0.0)
General disorders and administration site conditions									
Fatigue	10 (41.7)	2 (8.3)	0 (0.0)	9 (37.5)	1 (4.2)	0 (0.0)	21 (36.8)	2 (3.5)	0 (0.0)
Infections and infestations									
COVID-19	3 (12.5)	0 (0.0)	0 (0.0)	4 (16.7)	0 (0.0)	0 (0.0)	9 (15.8)	0 (0.0)	0 (0.0)
Investigations									
Blood creatinine increased	7 (29.2)	0 (0.0)	0 (0.0)	7 (29.2)	0 (0.0)	0 (0.0)	14 (24.6)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders									
Arthralgia	3 (12.5)	0 (0.0)	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	7 (12.3)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)									
Acute myeloid leukaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Myelodysplastic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8) *	0 (0.0)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Vascular disorders									
Hypertension	1 (4.2)	2 (8.3)	0 (0.0)	4 (16.7)	3 (12.5)	0 (0.0)	5 (8.8)	11 (19.3)	0 (0.0)

Legend: N: Number of patients. G: Grade.
*: Grade 4
Note. The entire RADAR cohort includes the randomized RADAR 200 mg arm and both non-randomized arms (200 mg and 300 mg).

the randomized standard 300 mg/day arm).

One case of myelodysplastic syndrome and one of acute myeloid leukaemia were reported, and occurred in the non-randomized RADAR arms. The investigators assessed these events as likely related to niraparib. One patient experienced a case of pancreatic cancer, evaluated as unlikely related to niraparib by the investigator. Acute myeloid leukaemia and pancreatic cancer had a fatal outcome.

4. Discussion

The NEWTON trial met its primary objective: the RADAR dosing of niraparib for patients with PSROC showed a statistically significant reduction in the rate of grade ≥ 3 thrombocytopenia compared with standard dosing.

ENGOT-ov16/NOVA trial had shown that niraparib 300 mg/day greatly improved the PFS in patients with PSROC but with a high haematologic toxicity burden, particularly grade ≥ 3 thrombocytopenia, which was higher than with other PARP inhibitors [16]. Retrospective analyses of niraparib studies identified two factors highly correlated with haematologic toxicity: body weight and platelet count. These results informed the SmPC and the amendment of the ENGOT-ov26/GOG-3012/PRIMA trial in newly diagnosed advanced OC. In the SmPC, the dose of niraparib was decreased to 200 mg in patients with body weight ≤ 58 kg, while in the PRIMA trial, the starting dose of 300 mg/day was reduced to 200 mg/day in patients with body weight < 77 kg or baseline platelet count $< 150000/\mu L$ [17].

Our trial is the first to compare the occurrence of grade ≥ 3 thrombocytopenia, randomizing the cohort of patients with body weight within 58–77 kg or a baseline body weight ≥ 77 kg and a platelet count $< 150{,}000/\mu L$ to 200 mg/day or 300 mg/day dosage.

The grade ≥ 3 thrombocytopenia rate during the first three cycles was 10.5% in the entire RADAR group, and it was reduced from 41.7% in the 300 mg/day arm to 4.2% in the RADAR 200mg/day randomized arm. Such a difference was statistically significant and its magnitude appeared consistent with a secondary analysis of the PRIMA trial [17].

In our study, as anticipated, most of the grade ≥ 3 thrombocytopenia occurred during the first 3 cycles; notably, only one case was diagnosed after the third cycle in the RADAR cohort. Of note, although the RADAR 300 mg/day cohort, comprising patients with body weight > 77 kg and baseline platelet count $\geq 150{,}000/\mu L$, experienced a low incidence of grade ≥ 3 thrombocytopenia (3 of 16 patients, 18.8%) 14 of 16 patients (87.5%) nonetheless required a dose reduction to 200 mg, predominantly due to grade 2 or 3 adverse events (8 of 14).

Severe hematologic toxicities, though monitored and managed clinically, required a higher rate of dose reductions and interruptions in the entire 300 mg/day cohort than in the RADAR 200 mg/day cohort and this, in turn, implies that the overall dose exposure during the treatment was similar in the two cohorts. Again, this finding is in keeping with other retrospective [12] and prospective studies [18].

Our study was not powered to demonstrate an equivalence in efficacy between the RADAR and the 300 mg/day dosing arms, but PFS and OS were numerically similar, and the overall performance of RADAR cohort, mirroring the NOVA population, was aligned with the NOVA's PFS and OS results.

Recent evidence suggests a clinically relevant relationship between PARP inhibitor exposure and both toxicity and efficacy outcomes. In BRCA-mutated ovarian cancer patients treated with olaparib, higher drug exposure has been associated with an increased risk of early haematological toxicity [19]. Similarly, exposure–response analyses for rucaparib demonstrated correlations between plasma concentrations, efficacy endpoints, and safety outcomes [20]. In addition, the NiQoLe trial [21,22] provided real-world data on niraparib in platinum-resistant ovarian cancer, and its ancillary pharmacokinetic analysis reported an association between early drug exposure (Day 8) and dose-limiting toxicities. These findings support the rationale for optimizing dosing strategies and potentially implementing therapeutic drug monitoring approaches.

In contrast with this evidence, no association was observed between

niraparib peak levels and grade ≥ 3 thrombocytopenia. In our study trough concentrations were significantly associated with serum creatinine and body weight, suggesting that patient-specific factors influence drug pharmacokinetics and therefore drug exposure. These findings should require confirmation in larger patient cohorts.

This study has several limitations; the premature closure of enrollment resulted in a reduced sample size and this limited the precision of the reduction estimate of thrombocytopenia incidence. Moreover, the PK analyses were exploratory and based on a limited number of samples and peak exposure was approximated using a 2-hour post-dose concentration, although the true maximum concentration occurs approximately 4–6 h after dosing. This factor and the sparse, non-optimal sampling schedule likely limited our ability to detect the exposure–toxicity relationship described in the literature.

In conclusion, an individualized RADAR dosing strategy was associated with a significant reduction in grade ≥ 3 thrombocytopenia compared with a fixed 300 mg/day starting dose, without an apparent compromise in efficacy.

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CRediT authorship contribution statement

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116685.

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