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Randomized phase II trial of weekly paclitaxel vs. cediranib-olaparib (continuous or intermittent schedule) in platinum-resistant high-grade epithelial ovarian cancer

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HIGHLIGHTS

- The superiority of cediranib-olaparib combination over the standard chemotherapy was not demonstrated.
- The intermittent schedule did not show any toxicity benefit and it seemed to have a lower activity than the continuous.
- Despite the negative result, cediranib-olaparib combination is an active and feasible non-chemotherapy oral regimen.

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ABSTRACT

Background. Previous findings showed that cediranib-olaparib increased PFS in women with recurrent platinum-sensitive ovarian cancer compared to olaparib alone.

Methods. BAROCCO trial randomized 123 patients: 80 mg/m2 paclitaxel weekly up to 24 weeks (control), olaparib 300 mg tablets twice daily together with 20 mg cediranib daily (continuous schedule) or with 20 mg cediranib 5 days/week (intermittent schedule) until progression. The primary objective was the PFS comparison between each experimental arm and the control (alpha one-sided 5%; power 80%; HR 0.5).

Results. The median platinum-free interval was 1.9 months, 60% of patients had been pretreated with 3 or more chemotherapy lines. Median PFS for paclitaxel, the continuous, and the intermittent schedules were 3.1, 5.6, and 3.8 months. The HR for PFS in the continuous arm vs control was 0.76 (90% CI: 0.50–1.14, $p = 0.265$). The HR for PFS in the intermittent arm vs control was 1.03 (90% CI: 0.68–1.55, $p = 0.904$). Treatment was discontinued due to adverse events in 15%, 20%, and 5% of patients in the control, continuous and intermittent arms. Grade ≥ 3 anemia and diarrhea and hypertension of any grade occurred only in the experimental arms, and peripheral neuropathies and alopecia only in the control arm. Five serious adverse drug reactions occurred and two were fatal: one in the control and one in the continuous arm.

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Conclusions. The combination of cediranib-olaparib was not superior to chemotherapy in terms of PFS in heavily pretreated platinum-resistant ovarian cancer patients. However, this oral doublet, is active and may offer a non-chemotherapy option in this difficult to treat population.

Clinical trial identification. IRFMN-OVA-7289, EudraCT: 2016–003964-38, NCT03314740.

1. Introduction

Relapses for which platinum is not the best option (platinum-resistant ovarian cancer [PROC] patient) are frequent [1] and tend to show poor chemo-responsiveness also to non-platinum agents. This setting represents a highly unmet medical need and investigating new therapeutic strategies is warranted. Currently, the treatment of PROC consists of single agents such as pegylated liposomal doxorubicin, weekly paclitaxel, gemcitabine, and topotecan, with median progression-free survival (PFS) of 3–4 months [2].

While antiangiogenic agents and Poly (ADP-ribose) polymerase (PARP) inhibitors are radically changing the therapeutic algorithm of ovarian carcinoma responsive to platinum, their evidence of efficacy in PROC patients is limited and, when this trial was designed, really scant.

The AURELIA trial reported a significant improvement in PFS with the addition of bevacizumab to chemotherapy in PROC patients (HR = 0.48, 95% CI: 0.38 to 0.60), the median PFS was 3.4 months with chemotherapy versus 6.7 months with the combined regimen [3]. However, bevacizumab for PROC has been not uniformly approved by drug regulatory agencies worldwide.

Kaufman et al. enrolled 193 carriers of the germline BRCA1/2 mutation (gBRCAm) with heavily pretreated platinum-resistant relapsed OC and found that olaparib was as active as monotherapy, with a 31%. response rate [4].

The combination of antiangiogenic agents with PARP inhibitors is of great interest in OC. In fact our trial was planned after Liu JF et al. reported their results for the combination of cediranib, an antiangiogenic tyrosine kinase inhibitor, and olaparib in patients with platinum-sensitive relapsing OC. In that phase II randomized trial the median PFS was 16.5 months versus 8.2 months with the combined regimen compared to the treatment with olaparib alone (HR: 0.50, 95% CI: 0.30–0.83), and in the gBRCAwt or unknown subpopulation the PFS gain was even greater (HR: 0.31, 95% CI: 0.15–0.66) [5].

The burden of toxicity of this combination, especially gastroenteric, was high but increasing evidence based on the use of other tyrosine kinase inhibitors indicates that intermittent schedules can significantly reduce the incidence of adverse events [6–8].

Therefore, we designed this phase II trial in PROC patients to test the possible synergy between cediranib and olaparib and a possible positive impact on toxicity of an intermittent cediranib schedule.

2. Methods

2.1. Patients

Eligible patients had high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer resistant to platinum-based chemotherapy (relapsed/progressive disease within six months from last platinum-based chemotherapy). Patients with performance status 0–1, with measurable disease and at any line of treatment after the first without restrictions regarding the type of last-line chemotherapy, including paclitaxel, received at least six months before the trial began, were eligible.

Patients with previous progression to weekly paclitaxel and who had received prior treatment with cediranib were not eligible; previous treatment with bevacizumab or other antiangiogenic drugs was allowed.

2.2. Trial design

Eligible patients were randomized with a 1:1:1 ratio to receive: 80 mg/m^2 of paclitaxel weekly (control arm) or 600 mg of olaparib (300 mg tablets twice daily) together with 20 mg of cediranib daily every day (continuous schedule); or olaparib 600 mg (300 mg tablets twice daily) every day together with 20 mg cediranib daily 5 days a week (intermittent schedule).

Treatment was continued until progression, unacceptable toxicity, patient's or physician's decision, death or for weekly paclitaxel only, up to 24 weeks.

Randomization used a biased-coin minimization procedure having as stratification factors gBRCA1-2 status (mutated vs. wild-type vs. unknown), prior chemotherapy (1–2 vs. ≥ 3 lines) and previous treatment with antiangiogenic drugs (yes vs. no). For patients assigned to control arm, cross-over at disease progression to receive olaparib and cediranib was not allowed. The Sponsor was responsible for randomization system and the electronic data capture system.

The primary endpoints were PFS and the number of evacuations per day over the first four weeks of treatment. Progressive disease (PD) was established as radiological disease progression according to RECIST 1.1 or as clinical progression if radiological evaluation was not feasible on account of clinical condition.

Disease assessments were done every 8 weeks until PD or up to 48 weeks whichever occurred first, and every 12 weeks thereafter. After PD, patients continued to be followed up for survival every 12 weeks.

Two PFS comparisons were planned for the primary efficacy analysis: 1) the continuous schedule of cediranib and olaparib vs. paclitaxel; 2) the intermittent schedule of cediranib and olaparib vs. paclitaxel. According to a hierarchical approach, the safety comparison of the number of evacuations between continuous and intermittent regimens was performed only if both experimental arms were superior to paclitaxel monotherapy in terms of PFS.

Secondary endpoints were: treatment compliance in terms of number of administered cycles; reasons for discontinuation and treatment modification; objective response rate (ORR), defined as the percentage of patients with an objective response (complete [CR] or partial response [PR]) as defined by RECIST 1.1, PFS2 defined as time from randomization to second disease progression according to RECIST 1.1 or clinical assessment, or death by any cause; overall survival (OS), defined as the time from randomization to the date of death for any cause; quality of life assessed with the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire. Although CA-125 was measured in this study it was not directly used for assessing objective response or progression. Patients continued the treatment until radiological disease progression as defined by RECIST 1.1, independently from CA-125 value. The main endpoint for HRQoL analysis was the Trial Outcome Index (TOI), an index derived from the FACT-O questionnaire and considered to target the main symptoms assessed by an ovarian cancer-related symptoms (ADD) subscale, together with function and physical wellbeing (FWB and PWB) subscales. HRQoL subscale scores ranged from 0 to 48 with higher scores indicating better HRQoL [9]. The questionnaire was administered at baseline-T0, at 4 weeks-T1, 8 weeks-T2 and 12 weeks-T3 or at treatment discontinuation whichever came first.

Safety endpoints were described as: for each drug-related adverse event the maximum grade experienced by each patient according to

NCI-CTCAE v. 4.0; for each drug-related adverse event, patients experiencing grade 3–4 events. If the same drug-related adverse event occurred two or more times in the same patient, this was counted as a single event and the worst grade was considered.

Moreover type, frequency and nature of Serious Adverse Events (SAEs), patients with at least one SAE, patients with at least one Serious Adverse Drug Reaction (SADR), patients with at least one Suspected Unexpected Serious Adverse Events (SUSAR) were described.

2.3. Sample size

Assuming a median PFS in the control arm of 3.4 months [3] this study was designed to detect a HR of 0.51, which corresponds to an advantage of 3.3 months in median PFS. To preserve a one-sided family-wise error rate of 10% the alpha error allocated to each comparison was 5% one-sided. With at least 80% power and the one-sided 5% significance level, for each comparison 55 events were needed. Considering the two pre-planned comparisons (intermittent vs paclitaxel and continuous vs paclitaxel), an enrolment of 18 months, a follow-up of 12 months, and a 10% of patients not evaluable for the primary endpoint, it was planned to enroll approximately 100 patients.

A mean reduction of two evacuations a day in the first four weeks of treatment was considered clinically relevant. The sample size calculated for PFS comparison should detect an effect size equal to 1 (assuming a standard deviation of 2) with power ≥ 90% and a one-sided first-type error of 5%.

2.4. Statistical analysis

PFS was primary assessed in the intention-to-treat (ITT) population. The ITT set was defined as all randomized patients with no major violations of eligibility criteria, and patients were analyzed according to randomization arm. The PP set was defined as all patients in the ITT set, who received at least four weeks of treatment, unless they interrupted it sooner for disease progression or death. Patients randomized to the control arm but receiving the experimental treatment, and patients randomized to the experimental arm but receiving the control treatment, were excluded from the PP population. Patients in the ITT population who received at least one dose of study treatment and had at least one radiological assessment were considered for the evaluation of the ORR (ORR population). All subjects in the ITT analysis set who completed at least the FACT-O questionnaires at T0 were included in the patient reported outcome (PRO) population. Safety endpoints were assessed in all patients in the ITT analysis set, who received at least one dose of study treatment, whether withdrawn prematurely or not. Patients were considered in the treatment arm they actually received (safety analysis set).

Continuous variables were expressed as medians with their first quartile (Q1) and third quartile (Q3); categorical variables were described including the frequency and percentage of subjects in each category.

Survival curves (PFS, OS, PFS2) were described with the Kaplan-Meier (KM) method. KM estimates for median and quartile event times were calculated. A Cox regression model was used to assess the reduction of risk in the differences in PFS, PFS2 and OS between arms, by including stratification variables and other clinical-biological features as covariates. Results were presented as hazard ratios (HR) and their 95% confidence intervals (CI) except for the primary endpoint for which the 90%CI were applied according to type I error allocated to each comparison (5% one-sided). The proportional hazards assumption was tested and if the assumption was not respected the survival curves were compared using the restricted mean survival time (RMST), even if this method was not specified in the protocol.

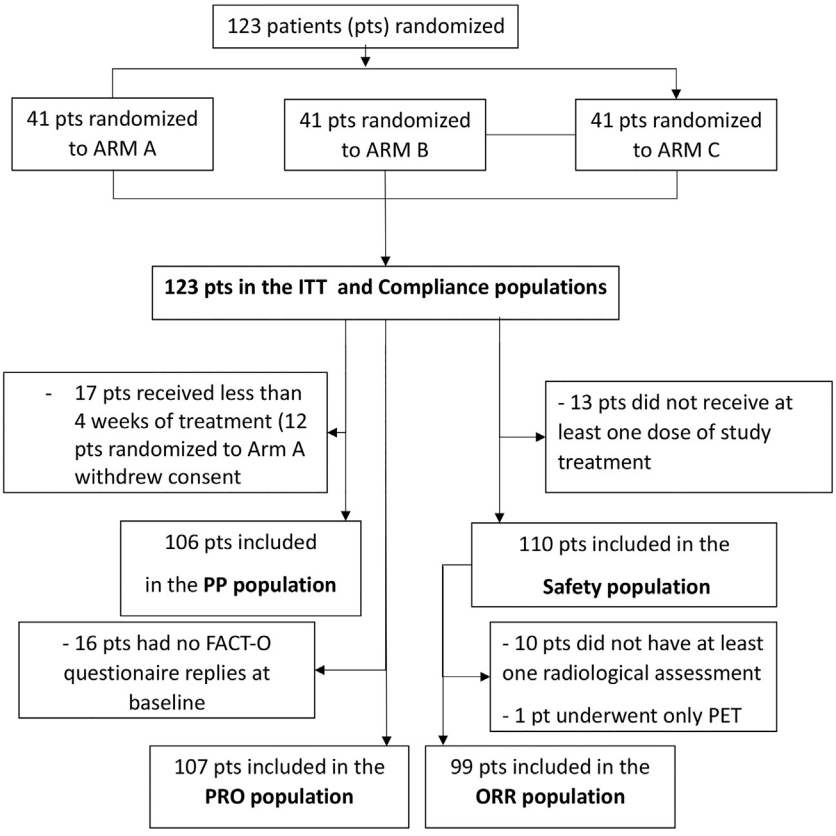

Fig. 1. Consort Diagram.
ARM A: paclitaxel; ARM B: cediranib+olaparib continuous schedule; ARM C: cediranib+olaparib lintermittent schedule; ITT: intention-to-treat; PP: per-protocol; ORR objective response rate; PRO: patient reported outcome.

Response to treatment was measured as the absolute and relative frequencies of patients with complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to RECIST 1.1. 95% CIs for response rates were computed with exact binomial methods.

HRQoL was assessed using changes in FACT-O scores between baseline (T0) and each visit (T1-T3) including the time of study discontinuation. A mixed model was used to assess differences in quality of life scores among arms, during time and to assess the effect of interaction between time and treatments.

All analyses were done with SAS software, version 9.4 (SAS Institute).

The study sponsor was the Mario Negri Institute in Milan, responsible for study design, conduction, data management, monitoring and statistical analysis. Astrazenca supported the study with an unrestricted grant and providing the study drugs (olaparib and cediranib). The study complied with the Declaration of Helsinki and with Good Clinical Practice guidelines; it was approved by the Italian competent authority and the ethics committees of all sites. All participants provided written informed consent before enrollment.

3. Results

From May 2017 to October 2018, a total of 123 patients, from seven experimental centers in Italy, were randomly assigned to paclitaxel (41), to the continuous schedule (41) or the intermittent schedule (41).

After randomization 12 patients assigned to the control arm withdrew their informed consent as they wanted to receive the standard therapy closer to their home. Because of the high attrition rate in the control arm, enrollment continued beyond the estimated 100 patients to achieve the number of evaluable patients required by the sample size. Fig. 1 shows the CONSORT diagram of the patient populations. Demographic and tumor characteristics, stratification factors are summarized in Table 1 and were well balanced among study groups.

At the time of analysis all patients had ended treatment. Twenty-one (78%), 32 (78%) and 38 (93%) in the control arm, continuous arm and

Table 1
Patients and tumor characteristics.

	paclitaxel $N = 41$	cediranib + olaparib continuous $N = 41$	cediranib + olaparib intermittent $N = 41$	overall $N = 123$
Age				
Median (Q1-Q3)	62.5 (56.6–69.7)	64.2 (54.0–68.4)	59.9 (54.6–68.4)	62.5 (55.2–69.3)
Performance status - n (%)				
0	33 (84.6)	36 (90.0)	30 (76.9)	99 (83.9)
1	6 (15.4)	4 (10.0)	9 (23.1)	19 (16.1)
Missing	2	1	2	5
Race - n (%)				
Asian	0 (0.0)	1 (2.4)	1 (2.4)	2 (1.6)
Black	1 (2.4)	0 (0.0)	0 (0.0)	1 (0.8)
Caucasian	36 (87.8)	38 (92.7)	40 (97.6)	114 (92.7)
Other	4 (9.8)	2 (4.9)	0 (0.0)	6 (4.9)
BRCA genes mutational status - n (%)				
Still Unknown	1 (2.4)	2 (4.9)	3 (7.3)	6 (4.9)
Wild Type	36 (87.8)	32 (78.0)	34 (82.9)	102 (82.9)
Mutated	4 (9.8)	7 (17.1)	4 (9.8)	15 (12.2)
Previous treatment with antiangiogenic drugs - n (%)				
No	19 (46.3)	19 (46.3)	19 (46.3)	57 (46.3)
Yes	22 (53.7)	22 (53.7)	22 (53.7)	66 (53.7)
Previous chemotherapy lines - n (%)				
Up to 2 lines	17 (41.5)	16 (39.0)	16 (39.0)	49 (39.8)
Three or more lines	24 (58.5)	25 (61.0)	25 (61.0)	74 (60.2)
Time from diagnosis (years)				
Median (Q1-Q3)	1.9 (1.1–2.9)	2.4 (1.4–4.6)	2.5 (1.3–4.0)	2.2 (1.3–4.0)
Missing	9	0	1	10
Primary Site - n (%)				
Fallopian	4 (12.5)	2 (4.9)	0 (0.0)	6 (5.3)
Ovary	27 (84.4)	38 (92.7)	40 (97.6)	105 (92.1)
Peritoneal	1 (3.1)	1 (2.4)	1 (2.4)	3 (2.6)
Missing	9	0	0	9
F.I.G.O. Stage - n (%)				
I-II	1 (3.3)	2 (5)	5 (12.5)	8 (7.2)
III	20 (66.7)	25 (62.5)	25 (62.5)	70 (63.6)
IV	6 (20.0)	12 (30.0)	9 (22.5)	27 (24.5)
Unknown	3 (10.0)	1 (2.5)	1 (2.5)	5 (4.5)
Missing	11	1	1	13
Histological Type - n (%)				
Clear cell	3 (9.4)	2 (4.9)	4 (9.8)	9 (7.9)
Endometrioid	1 (3.1)	3 (7.3)	3 (7.3)	7 (6.1)
Mixed epithelial	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.9)
Serous	28 (87.5)	34 (82.9)	34 (82.9)	96 (84.2)
Unknown	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.9)
Missing	9	0	0	9
Size of residual disease after primary surgery - n (%)				
> 1 cm	4 (12.9)	6 (15.0)	5 (12.2)	15 (13.4)
≤ 1 cm	22 (71.0)	23 (57.5)	27 (65.9)	72 (64.3)
Unknown	5 (16.1)	11 (27.5)	9 (22.0)	25 (22.3)
Missing	10	1	0	11
Last platinum-free interval (months)				
Median (Q1-Q3)	3.0 (0.6–5.4)	2.2 (0.7–4.3)	1.5 (0.7–3.2)	1.9 (0.7–4.3)

Legend: N: number of subjects, Q1-Q3: First - third quartile. *3 patients progressed during platinum-based therapy.

Table 2
Treatment compliance.

	Paclitaxel $N = 41$	Cediranib + olaparib continuous $N = 41$	Cediranib + olaparib intermittent $N = 41$	Overall $N = 123$
Never started - n (%)	13 (31.7)	0 (0.0)	0 (0.0)	13 (10.6)
Reasons:				
Consent withdrawn/Patient refusal	12 (92.3)	–	–	12 (92.3)
Deterioration of clinical conditions	1 (7.7)	–	–	1 (7.7)
Treatment discontinued - n (%)	27 (65.9)	41 (100)	41 (100)	109 (88.6)
Reasons for discontinuation:				
Adverse event	4 (14.8)	8 (19.5)	2 (4.9)	14 (12.8)
Death related to toxicity	1 (3.7)	0 (0.0)	0 (0.0)	1 (0.9)
Disease progression	21 (77.8)	32 (78.0)	38 (92.7)	91 (83.5)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.9)
Subject refusal	1 (3.7)	1 (2.4)	0 (0.0)	2 (1.8)
Treatment completed - n (%)	1 (2.4)	NA	NA	1 (0.8)
Number of cycles				
Median (IQR)	4.0 (2.0–6.0)	5.0 (3.0–8.0)	5.0 (3.0–7.0)	4.0 (3.0–7.0)
Min – Max	1.0–14.0	1.0–21.0	1.0–17.0	1.0–21.0

Legend: N: number of subjects, NA: Not Applicable, IQR: First - third quartile.

intermittent arm, discontinued treatment for disease progression while 4 (15%), 8 (20%) and 2 (5%) discontinued because of adverse event (Table 2). One patient stopped because of a fatal adverse event related to treatment.

3.1. Progression-free survival

With a median follow-up of 29.7 months (Q1-Q3: 20.7–31.2) disease progression or death occurred in 107 out of 123 patients. KM estimates for median PFS in the ITT population were 3.1 months in the control arm (Q1-Q3: 1.9–6.3), 5.6 months in the continuous arm (Q1-Q3: 3.2–7.4) and 3.8 months in the intermittent arm (Q1-Q3: 2–5.8) (Fig. 2 (panel A)).

The Cox regression model showed no significant difference in PFS between the continuous and control arms (HR: 0.76, 90% CI: 0.50–1.14, $p = 0.265$); however, there was clear evidence of non-proportional hazards (test for proportional hazard $p = 0.016$). For the difference in RMST there was an advantage in the effect of the continuous arm of 1.25 months, although not statistically significant, (95% CI: −0.32-2.82, $p = 0.119$; truncation time: 12.8 months). Regarding the comparison in terms of PFS between the intermittent and control arms, the Cox model showed no significant difference (HR: 1.03, 90% CI: 0.68–1.55, $p = 0.904$). For this comparison, the assumption of proportional hazards was respected ($p = 0.33$).

Results on PP population are superimposable to that on ITT population (Fig. 2, panel B).

Multivariable Cox models considering stratification factors and age as covariates did not show any significant results in the ITT and PP populations (Table S1).

The forest plot summarizing the subgroup analyses of stratification factors is presented in Fig. 3. In the subgroup gBRCAwt or unknown ($n = 108$) the estimates of median PFS for paclitaxel, the continuous, and the intermittent arms were 2.1 months (Q1-Q3: 1.9–6), 5.6 months (Q1-Q3: 3.8–8.7) and 3.8 months (Q1-Q3: 2.0–5.7). The HR for PFS in the continuous arm versus the control was 0.65 (95% CI: 0.38–1.10, $p = 0.108$), HR for PFS in the intermittent arm versus control was 0.90 (95% CI: 0.53–1.51, $p = 0.681$) (Fig. 2, panel C).

3.2. Response

Ninety-nine patients were analyzed for ORR (24 in the control arm, 39 in the continuous and 36 in the intermittent arms). Nine patients (38%) had ORR (CR + PR) in the control arm, 6 (15%) in the continuous and 4 (11%) in the intermittent arms with a statistically significant difference in favor of the control arm for both comparisons ($p = 0.047$ and 0.016 for the continuous arm versus control arm and intermittent arm versus control arm). Table S2 shows frequencies and 95% CI for response rates.

3.3. Progression-free Survival-2

Out of 106 patients of the PP population, 39 (37%) did not receive any chemotherapy after the BAROCCO treatment study; 50 (47%) received one subsequent line, 13 (12%) 2 lines and 4 (4%) 3 subsequent lines. The majority received a subsequent line with a monotherapy without platinum (72% of the first subsequent line, 77% for the second subsequent line and 100% for the third subsequent line). Table S3 shows the lines after the BAROCCO treatment.

Ninety-five patients (77%) out of 123 had a second progression or died. Median PFS2 was 8.8 months (Q1-Q3: 6.9–21.5) for the control arm, 11.6 months (Q1-Q3: 8.4–18.4) for the continuous arm and 9.6 months (Q1-Q3: 5.5–14.1) for the intermittent arm. The HR for PFS2 in the continuous vs. the control arm was 0.85 (95% CI: 0.5–1.42, $p = 0.527$), HR for PFS2 in the intermittent arm vs. control arm was 1.08 (95% CI: 0.65–1.79, $p = 0.780$). The proportional hazard assumption was respected for both comparisons ($p = 0.417$ and 0.426). Fig. S2, panel A shows the KM curves of PFS2 for the ITT Analysis Set. Fig. S3, panel A shows the KM curves of PFS2 for the PP Analysis Set.

Out of 123 patients, 89 patients died (72%). The reason was mainly PD (85 patients, 96%), adverse events related to treatment in 2 cases (2%) and 2 patients (2%) died for other reasons. KM estimates for median OS was 9.3 months (Q1-Q3: 7.4–21.5) for the control arm, 11.6 months (Q1-Q3: 8.4–23) for the continuous arm and 9.6 months (Q1-Q3: 5.5–14.1) for the intermittent arm. HR for OS in the continuous arm vs. the control arm was 0.86 (95% CI: 0.8–1.46, $p = 0.572$, test for proportional hazards $p = 0.570$) and HR for OS in the intermittent arm vs. the control arm was 1.13 months (95% CI: 0.67–1.92, $p = 0.637$, test for proportional hazards $p = 0.484$). Fig. S1, panel B shows the KM curves of OS for the ITT analysis set. Fig. S2, panel B shows the KM curves of OS for the PP analysis set.

Out of 107 patients who completed the FACT-O questionnaire at T0, 93 (87%) also completed it at T1, 78 (80%) at T2 and 67 (91%) at T3.

HRQoL declined over time except for the emotional wellbeing subscale. Each subscale is depicted in Fig. S3. TOI scores declined over time. The worsening in the HRQoL seemed to be driven by the ADD subscale. There were no differences in QoL between arms as the mixed model showed that the treatment arms and the interaction between time and treatment had no statistically significant effect on quality of life (Table S4 for details).

No primary safety analysis in terms of gastrointestinal events between continuous and intermittent arm was done because neither experimental arm showed any superiority in PFS over the control arm.

For treatment tolerability 110 patients were considered: 28 patients assigned to paclitaxel, 41 to the continuous schedule and 41 to the intermittent schedule. In all, 660 adverse events were reported, 448 drug-related, 89 in the paclitaxel arm, 216 in the continuous arm and 143 in

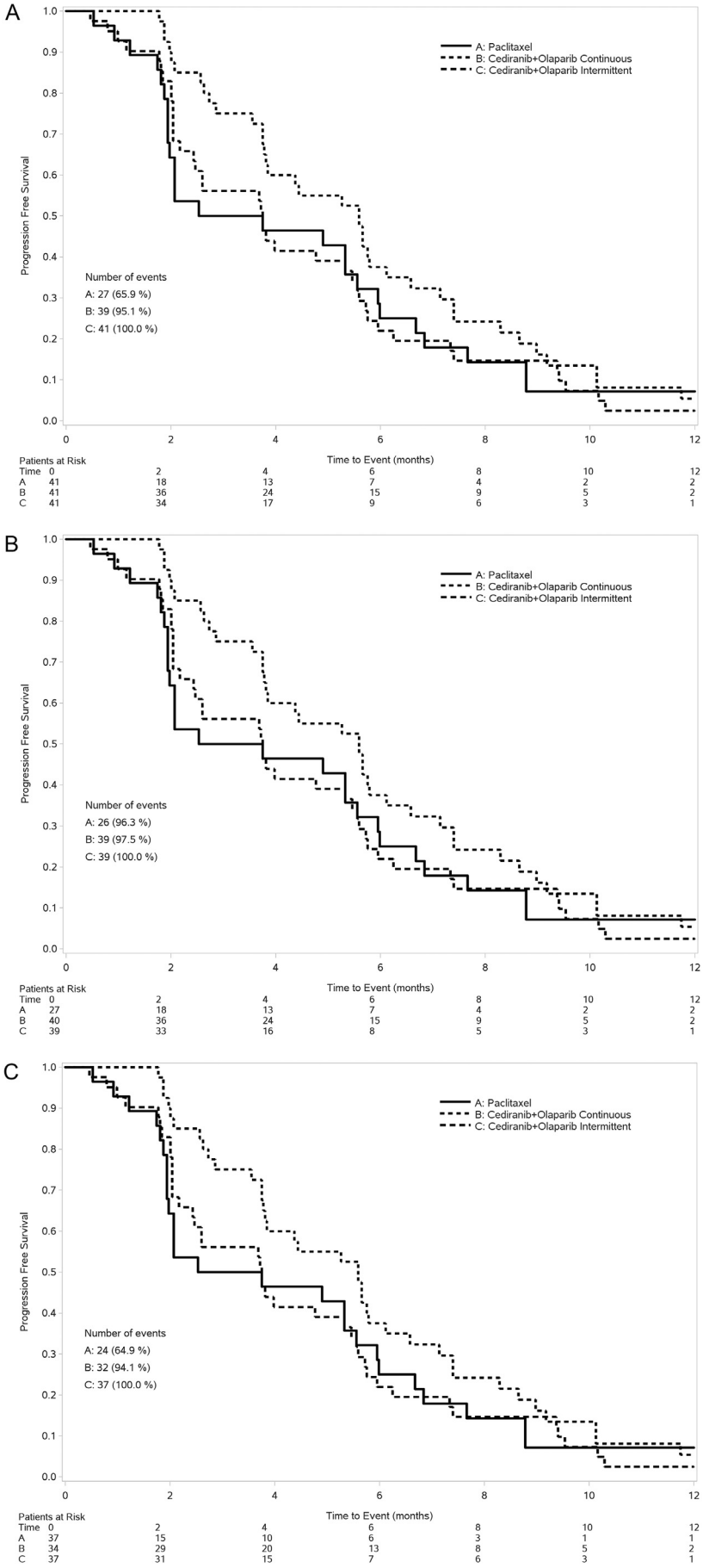

Fig. 2. Kaplan-Meier display of Progression Free Survival for ITT Analysis Set (panel A) and for PP Analysis Set (panel B) and for BRCA Wild Type or Unknown (panel C).

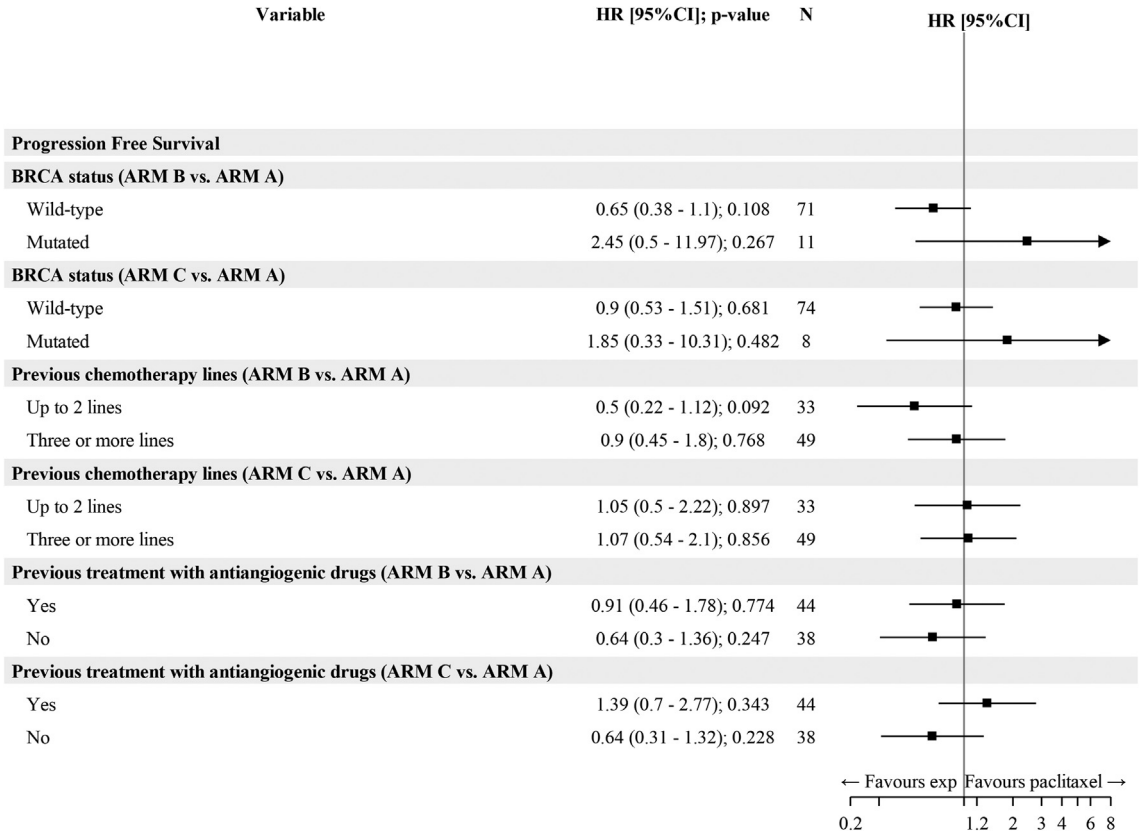

Fig. 3. Forest plot for PFS in the subgroups analysis of stratification factors.
Arm A:paclitaxel; Arm B: continuous schedule; Arm C: intermittent Schedule.

the intermittent one; 79 out of the 448 (17.7%) were grade ≥ 3: 11 in the paclitaxel arm, 35 in the continuous arm and 33 in the intermittent arm. In total 84 patients had at least one drug-related adverse event, 19 (23%), 34 (41%) and 31 (37%) in the paclitaxel, continuous and intermittent arms.

Table 3 lists the frequency of drug-related adverse events of any grade that occurred in at least 10% of patients and the drug-related adverse events of grade ≥ 3 regardless of their frequency. The most frequent drug-related adverse events of any grade observed in the experimental arms were nausea, vomiting and fatigue. Anemia and diarrhea of grade ≥ 3 and hypertension of any grade occurred only in the experimental arms. Peripheral neuropathies and alopecia were observed only in the control arm.

Twenty-eight SAEs were reported: 4 in 3 subjects in the paclitaxel arm, 12 in 11 subjects in the continuous arm and 12 in 9 subjects in the intermittent arm. Five of the 28 SAEs were considered related to the study drugs (SADRs). Two SADRs were fatal: one patient in the control arm died of sepsis and one patient in the continuous arm died of myelodysplastic syndrome. Two out 5 SADRs were considered unexpected (SUSAR): pneumonitis grade 3 and the fatal myelodysplastic syndrome, both in the continuous arm, and considered by the investigators as related to olaparib.

4. Discussion

This phase II randomized trial failed to show any superiority in efficacy of the cediranib and olaparib combination over the standard of care for patients with PROC.

The intermittent schedule did not show any benefit in the toxicity profile and unexpectedly it seemed to have a lower activity than the continuous schedule.

Although OC can respond to several lines of platinum-based regimens, the final step of its natural history is the platinum resistance. At this stage the outlook is dismal with median survival approximately 12 months. Many clinical trials have explored chemotherapy alternatives to platinum but with limited success and showing that multidrug regimens were no better and more toxic than single agents. The combination of a single cytotoxic agent with a biological agent, bevacizumab improved PFS but failed to show any survival benefit [3]. The CLIO study compared olaparib monotherapy with chemotherapy in PROC patients and olaparib showed a favorable objective response rate (18% vs 6%) [10]. The single arm QUADRA trial [11] for late-line treatment of OC gave that single-agent niraparib in the 312 PROC patients showed an overall objective response as high as 27% in the BRCAm and as low as 3% in the HRD-negative/unknown patients.

On the biological basis, the synergistic effect of cediranib-olaparib seems to be due to the down-regulation of some genes involved in the homologous recombination system induced by cediranib which, in turn, potentiate the effect of olaparib [12]. Recent findings from patient-derived ovarian cancer xenografts confirmed an additive combination benefit in tumors poorly-sensitive to platinum and olaparib although this combination effect was mostly driven by targeting independent mechanisms [13].

However, the PROC remains a formidable challenge to clinical research as the tumor complexity in this final stage presents extreme cellular heterogeneity, expressing several drug resistance and immune evasion mechanisms. This may be the case of our study. The patients in our trial had a very poor prognosis as they had a median platinum-free interval < 3-months. Moreover, 60% of patients had already received three or more lines. This may explain why this drug combination, which had shown great activity in an earlier stage of the disease, underperformed in this late clinical setting. Liu et al. showed that the cediranib-olaparib combination doubled the PFS in comparison with olaparib alone in platinum-sensitive OC patients (HR = 0.50) and significantly prolonged OS in the gBRCA wt/unknown-subset (37.8 versus

Table 3
Adverse reactions that occurred in at least 10% of the patients and AR with Grade ≥ 3 SADR – Safety-2 population.

	paclitaxel (*N* = 28)	cediranib + olaparib continuous (*N* = 41)	cediranib + olaparib intermittent (*N* = 41)
Most common adverse reaction	N (%)		
Anemia			
Any grade	5 (17.9)	7 (17.1)	9 (22)
Grade ≥ 3	0 (0)	4 (9.8)	6 (14.6)*
Grade 5	0 (0)	0 (0)	0 (0)
Bone marrow hypocellular			
Any grade	0 (0)	1 (2.4)	0 (0)
Grade ≥ 3	0 (0)	1 (2.4)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Febrile neutropenia			
Any grade	0 (0)	0 (0)	1 (2.4)
Grade ≥ 3	0 (0)	0 (0)	1 (2.4)
Grade 5	0 (0)	0 (0)	0 (0)
Diarrhea			
Any grade	1 (3.6)	5 (12.2)	4 (9.8)
Grade ≥ 3	0 (0)	2 (4.9)	1 (2.4)
Grade 5	0 (0)	0 (0)	0 (0)
Mucositis oral			
Any grade	2 (7.1)	5 (12.2)	0 (0)
Grade ≥ 3	0 (0)	1 (2.4)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Nausea			
Any grade	5 (17.9)	23 (56.1)	20 (48.8)
Grade ≥ 3	0 (0)	1 (2.4)	3 (7.3)
Grade 5	0 (0)	0 (0)	0 (0)
Vomiting			
Any grade	0 (0)	17 (41.5)	15 (36.6)
Grade ≥ 3	0 (0)	0 (0)	2 (4.9)
Grade 5	0 (0)	0 (0)	0 (0)
Fatigue			
Any grade	7 (25)	21 (51.2)	17 (41.5)
Grade ≥ 3	0 (0)	4 (9.8)	5 (12.2)*
Grade 5	0 (0)	0 (0)	0 (0)
Sepsis			
Any grade	1 (3.6)	0 (0)	0 (0)
Grade ≥ 3	1 (3.6)	0 (0)	0 (0)
Grade 5	1 (3.6)*	0 (0)	0 (0)
Neutrophil count decreased			
Any grade	3 (10.7)	3 (7.3)	2 (4.9)
Grade ≥ 3	2 (7.1)	1 (2.4)	1 (2.4)
Grade 5	0 (0)	0 (0)	0 (0)
Platelet count decreased			
Any grade	0 (0)	3 (7.3)	1 (2.4)
Grade ≥ 3	0 (0)	1 (2.4)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
White blood cells decreased			
Any grade	1 (3.6)	2 (4.9)	0 (0)
Grade ≥ 3	1 (3.6)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Anorexia			
Any grade	0 (0)	2 (4.9)	1 (2.4)
Grade ≥ 3	0 (0)	1 (2.4)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Myelodysplastic syndrome			
Any grade	0 (0)	1 (2.4)	0 (0)
Grade ≥ 3	0 (0)	1 (2.4)	0 (0)
Grade 5	0 (0)	1 (2.4)*	0 (0)
Peripheral motor neuropathy			
Any grade	3 (10.7)	0 (0)	0 (0)
Grade ≥ 3	1 (3.6)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Peripheral sensory neuropathy			
Any grade	4 (14.3)	0 (0)	0 (0)
Grade ≥ 3	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Pneumonitis			
Any grade	0 (0)	1 (2.4)	0 (0)
Grade ≥ 3	0 (0)	1 (2.4)*	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Alopecia			
Any grade	5 (17.9)	0 (0)	0 (0)
Grade ≥ 3	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Palmar-plantar erythrodysesthesia syndrome			
Any grade	2 (7.1)	2 (4.9)	0 (0)
Grade ≥ 3	0 (0)	1 (2.4)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Rash maculo-papular			
Any grade	3 (10.7)	2 (4.9)	2 (4.9)
Grade ≥ 3	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Hypertension			
Any grade	0 (0)	12 (29.3)	8 (19.5)
Grade ≥ 3	0 (0)	5 (12.2)	6 (14.6)
Grade 5	0 (0)	0 (0)	0 (0)
Thromboembolic event			
Any grade	0 (0)	2 (4.9)	2 (4.9)
Grade ≥ 3	0 (0)	0 (0)	1 (2.4)
Grade 5	0 (0)	0 (0)	0 (0)

Legend: N: number of subjects. Adverse reactions were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, * One of these cases was reported as a Serious Adverse Drug Reaction (SADR).

23.0 months, $p = 0.047$) [14]. Even when the cediranib-olaparib combination was compared with chemotherapy in platinum-sensitive patients it improved PFS, although no significantly, (HR 0.86, 95%CI 0.66–1.11), apparently more in the BRCAm population (HR 0.55, 95%CI 0.73–1.30). In our trial a preplanned subgroup analysis suggested better performance of the combination in gBRCAwt patients but, unexpectedly, olaparib and cediranib failed in gBRCAm.

Based on the ICON6 study and in line with other combination phase 3 trials in lung cancer, colorectal cancer and glioblastoma [15–18], cediranib was given at a dose of 20 mg daily instead of 30 mg as in Liu et al.'s study [14] and this might explain the better toxicity profile: grade 3 or higher diarrhea, fatigue and hypertension were 25%, 27% and 41% in Liu et al.'s study and less than half in our continuous and intermittent arms.

Limitations of this trial include a sub-optimal comparison group, as weekly paclitaxel plus bevacizumab performed better than weekly paclitaxel alone in the AURELIA trial. In that trial most of the patients were bevacizumab-naïve as only 8% had had previous antiangiogenic therapy. In our trial, 53.7% of patients had already received bevacizumab. Bevacizumab was not considered standard practice in this setting and is therefore not reimbursed by the Italian National Health Service.

Another potential limitation regards the fact that twelve patients withdrew their consent after knowing they were assigned to the control arm. To overcome this issue, we continued randomization beyond the planned sample size in order to get the required number of informative patients. The PFS HRs comparing the experimental arms with control, from the multivariable Cox model, were similar to those from the univariable Cox model, suggesting that no serious imbalance between arms in the stratification factors has been introduced.

Finally, as inherent to many phase II trials, this one had a small sample and may have been underpowered to reach as a statistically significant a smaller but still clinically significant-gain in PFS.

In conclusion, the combination of cediranib-olaparib is a feasible oral regimen that shows promising activity. These results support ongoing trials investigating the same combination as an alternative to chemotherapy in PROC patients (NCT02502266/COCOS, NCT03117933/OCTOVA).

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' contribution

NC: Conceptualization, Investigation, Data Curation, Writing - Review & Editing;
FeT: Conceptualization, Investigation, Data Curation, Writing - Review & Editing;
PBP: Investigation, Data Curation, Writing - Review & Editing;
MON: Investigation, Data Curation, Writing - Review & Editing;
GeT: Investigation, Data Curation, Writing - Review & Editing;
AB: Investigation, Data Curation, Writing - Review & Editing;
AAL: Investigation, Data Curation, Writing - Review & Editing;
ADC: Investigation, Data Curation, Writing - Review & Editing;
ML: Investigation, Data Curation, Writing - Review & Editing;
RM: Investigation, Data Curation, Writing - Review & Editing;
IP: Investigation, Data Curation, Writing - Review & Editing;
GiT: Investigation, Data Curation, Writing - Review & Editing;
FrT: Data Curation, Writing - Review & Editing, Project administration;
MFA: Methodology; Formal analysis, Visualization, Writing - Original Draft.
ER: Methodology, Writing - Review & Editing;
DP: Data Curation, Writing - Review & Editing;
LC: Data Curation, Writing - Review & Editing;
RF: Methodology, Writing - Review & Editing;
VT: Methodology, Writing - Review & Editing;
EB: Data Curation, Methodology, Writing - Original Draft, Project administration;

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