Gynecologic Oncology 165 (2022) 14–22

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Randomized CLIO/BGOG-ov10 trial of olaparib monotherapy versus physician's choice chemotherapy in relapsed ovarian cancer

Adriaan Vanderstichele [a,b,1], Liselore Loverix [a,b,1], Pieter Busschaert [a,b,c,d], Els Van Nieuwenhuysen [a,b], Sileny N. Han [a,b], Nicole Concin [a,b], Tiene Callewaert [a,b], Siel Olbrecht [a,b], Rawand Salihi [a,b], Patrick Berteloot [a,b], Patrick Neven [a,b], Diether Lambrechts [c,d], Toon Van Gorp [a,b], Ignace Vergote [a,b,*]

[a] Belgium and Luxembourg Gynaecological Oncology Group (BGOG), Department of Gynaecology and Obstetrics, University Hospitals Leuven, Leuven, Belgium
[b] Laboratory of Gynaecological Oncology, Leuven Cancer Institute, KU Leuven, Leuven, Belgium
[c] Laboratory for Translational Genetics, Department of Oncology, KU Leuven, Leuven, Belgium
[d] Center for Cancer Biology, VIB, Leuven, Belgium

HIGHLIGHTS

- Phase II randomized study of olaparib monotherapy versus chemotherapy in recurrent ovarian cancer
- Objective response rate was overall similar in the total study (n = 160) for olaparib and chemotherapy
- In platinum-sensitive disease the response rate was numerically higher with chemotherapy
- Progression free survival, clinical benefit rate and overall survival were overall not significantly different.
- In platinum-resistant ovarian cancer with ≥4 prior lines, olaparib seemed to be more effective than chemotherapy.

ARTICLE INFO

Article history:
Received 5 November 2021
Received in revised form 21 January 2022
Accepted 27 January 2022
Available online 14 February 2022

Keywords:
Ovarian cancer
Recurrence
Randomized
PARPi
Olaparib
Chemotherapy

ABSTRACT

Objective. Comparison of olaparib (OLA) monotherapy versus chemotherapy in patients with platinum-sensitive (PSOC) or platinum-resistant ovarian cancer (PROC).

Methods. Patients with measurable disease and ≥ 1 prior line of chemotherapy (CT) were randomized 2:1 to OLA (300 mg tablets, BID) or physician's choice CT.: for PSOC: Carboplatin-Pegylated-Liposomal-Doxorubicin (PLD) or Carboplatin-Gemcitabine; for PROC: PLD, Topotecan, Paclitaxel or Gemcitabine.

Results. 160 patients (60 with PSOC and 100 with PROC) were randomized 2:1 to OLA ($n = 107$) or CT ($n = 53$). Baseline characteristics were similar between both arms. Overall objective response rate (ORR) for OLA and CT were similar (24.3% (26/107) and 28.3% (15/53), respectively). Clinical benefit rate (≥ 12 weeks) was similar with 54.2% (58/107) and 56.6% (30/53), respectively. In PSOC, ORR was 35.0% (14/40) and 65.0% (13/20) for OLA and CT ($p = 0.053$); in PROC, ORR was 17.9% (12/67) and 6.1% (2/33) for OLA and CT ($p = 0.134$). ORR in heavily pretreated PROC (>4 prior lines) was 22.9% (8/35) with OLA versus 0% (0/14) for CT. ORR of 35.7% (5/14) and 13.2% (7/53) was observed in BRCA-mutated and -wildtype PROC cases, respectively. Median PFS in PROC was not significantly different with 2.9 months (95% CI 2.8–5.1 in the OLA group versus 3.8 months (95% CI 3.0–6.4) in the CT group (hazard ratio [HR] 1.11 [95% CI 0.72–1.78]; log-rank $p = 0.600$).

Conclusion. OLA monotherapy showed overall an equal response rate in relapsed ovarian cancer compared with CT. In PROC, ORR and TFST tended to be higher with OLA than with CT. In heavily pretreated patients (four lines or more) with PROC disease, OLA treatment seemed to be more effective than CT.

1. Introduction

Women diagnosed with ovarian cancer between 2010 and 2014 still have a 5-year survival of less than 50% in most countries [1]. Although the 5-year survival rate has improved over the last 25 years, this is not confirmed when looking at long-term survival [2]. Hence, these findings

* Corresponding author at: Herestraat 49, 3000 Leuven, Belgium.
E-mail address: ignace.vergote@uzleuven.be (I. Vergote).
[1] Both authors contributed equally

https://doi.org/10.1016/j.ygyno.2022.01.034
0090-8258/

reflect a more prolonged disease control with current management rather than an increased cure rate. Indeed, patients with advanced OC are often exposed to multiple lines of chemotherapy (CT), although response rates in relapsed disease vary widely and cumulative toxicity remains a substantial problem in many patients.

Multiple clinical trials in relapsed OC evaluate the combination of CT with new agents targeting multiple oncogenic molecular pathways and processes such as angiogenesis, apoptosis, the immune response as well as DNA repair. OC is often characterized by preexisting defects in DNA damage repair and, more specifically, in defective double strand break repair by homologous recombination (HRR) as demonstrated by frequent presence of oncogenic *BRCA1/2* mutations [3]. The inhibition of poly(ADP-ribose) polymerase (PARP) proteins, involved in single-strand break repair and the regulation of double-strand break repair, leads to a higher dependency on HRR for maintaining genomic stability and cell survival. Cancer cells with HRR deficiency (homologous recombination deficiency (HRD)-positive cancers) will therefore be selectively targeted by PARP inhibitors [4]. Relapsed OC after multiple lines of treatment represents a clinical setting with limited treatment choices [5]. In the last decade, PARP inhibitors have revolutionized the contemporary treatment of advanced-stage and relapsed OC, especially in the maintenance setting after CT [4].

However, PARP inhibitor therapy may also be of value in chemotherapy-free treatment regimens for relapsed OC. Single-agent PARP inhibitor therapy for relapsed OC was FDA approved for BRCA1/2-mutated cases (olaparib and rucaparib) and HRD-positive cases (niraparib), based on the results of three single-arm phase II trials [6–8].

First, single-agent olaparib (OLA) therapy for germline BRCA1/2-mutated relapsed OC, treated with three or more lines of chemotherapy, showed a response rate of 34% in Study 42 [6]. Second, rucaparib received accelerated approval for single-agent treatment of both germline and somatic BRCA1/2-mutated relapsed OC, treated with at least two prior lines of CT. This was based on data from two open-label single-arm trials: Study 10 (part 2A) and ARIEL2 (part 1 and 2). Accelerated approval of rucaparib was based on a combined efficacy analysis from both trials [7]. In these combined analyses, almost 75% of patients had platinum-sensitive ovarian cancer (PSOC) and 25% platinum-resistant/refractory (PROC). All patients had either a germline or somatic BRCA1/2-mutation. All patients had at least two lines of prior platinum-based CT and 61% received at least three previous lines of chemotherapy. The response rate was 54% for all patients; 66% and 25% in PSOC and PROC, respectively. Finally, the approval of niraparib as single-agent was based on the results of the QUADRA trial [8].This trial evaluated the efficacy of niraparib in relapsed high-grade serous OC with measurable disease, after three or more prior lines of CT [8]. The primary objective was the efficacy evaluation of niraparib in a subpopulation of HRD-positive (including BRCAm) PSOC after three or four lines of treatment without previous PARP inhibitor treatment [8]. HRD testing was performed on the primary tumor, using the myChoice® HRD test by Myriad Genetics [9]. The response rate in the HRD positive PSOC population was 28%. Efficacy was also shown for HRD-positive PROC cases after four or more prior lines of treatment, with a response rate of 10%.

Despite the aforementioned data, there is still insufficient clinical data on single-agent PARP inhibitor treatment of relapsed OC. In this CLIO study, patients with both PSOC and PROC after one or more lines of prior treatment were randomized between single-agent OLA versus physician's choice CT and we report here the efficacy evaluation.

2. Methods

2.1. Study design and participants

The CLIO/BGOG-ov10 study (NCT02822157) was a prospective randomized, open-label, two-arm study in patients with relapsed epithelial OC. The trial was performed at the University Hospitals Leuven, Belgium, EU. The CLIO study was an investigator-initiated study under ENGOT model A [10]. University Hospitals Leuven was the sponsor and responsible for the study design, conduct and reporting. Eligible patients were adult (age 18 or above), female patients with recurrent epithelial carcinoma of the ovary, fallopian tube or primary peritoneum with the following histology: serous (high-grade), endometrioid (all grades allowed), clear-cell (all grades allowed), carcinosarcoma and undifferentiated carcinoma. All patients were treated with at least one previous line of CT and previous treatment with a PARP inhibitor was allowed. Patients with PSOC and PROC, based on the sensitivity to the last platinum-based CT (platinum-free interval of ≥6 and <6 months, respectively) were eligible. Patients with primary platinum-refractory disease (defined as first relapse or disease progression during or within 28 days of the last dose of platinum-based CT in primary treatment) were excluded. PSOC cases were excluded if the presence of a pathogenic germline or somatic BRCA1/2 mutation was known at the time of inclusion. However, consent to perform germline and somatic BRCA1/2 testing as part of the study was required. Measurable disease on CT imaging according to modified RECIST criteria v1.1 [11] was mandatory and archival tissue of the primary tumor (either fresh-frozen or FFPE) needed to be available. The study received ethical approval by the Ethical Committee of the University Hospitals Leuven (reference number S58891). All patients provided a written informed consent prior to any study specific procedures. All study procedures were performed in compliance with Good Clinical Practice and all applicable local laws.

2.2. Procedures

Patients were randomized in a 2:1 ratio to receive OLA monotherapy or physician's choice standard CT with the possibility of crossover at time of progression in the CT arm. Randomization was separately performed for patients with PSOC and PROC. OLA was given as tablets at a starting dose of 300 mg BID (2 × 150 mg tablets) continuously, beginning on day 1 and every cycle of 28 days thereafter until study discontinuation. Dose interruptions were allowed if required for a maximum of 28 days. Dose reductions to 250 mg BID and 200 mg BID were done according to dose modification guidelines. Patients with PSOC disease randomized to CT were treated with one of the following regimens: Carboplatin (AUC 4; on day 1) + Gemcitabine (1000 mg/m^2 on day 1 and 8) in 21-day cycles; Carboplatin (AUC 5; on day 1) + Paclitaxel (175 mg/m^2 on day 1) in 21-day cycles; Carboplatin (AUC 5; on day 1) + Pegylated Liposomal Doxorubicin (PLD; 30 mg/m^2 on day 1) in 28-day cycles. For PROC disease, the following regimens were possible: PLD (40 mg/m^2 on day 1) in 28-day cycles; Topotecan (1.25 mg/m^2 on day 1–5) in 21-day cycles; Paclitaxel (80 mg/m^2 on day 1, 8 and 15) in 28-day cycles; Gemcitabine (1000 mg/m^2 on day 1, 8 and 15) in 28-day cycles. Tumor assessment was performed every 12 weeks via computed tomography imaging of the thorax, abdomen and pelvis. Safety monitoring was performed every four weeks. Adverse events were classified and graded according to the NCI Common Terminology Criteria for Adverse Events (version 5.0) [12]. Patient-reported outcomes (EORTC QLQ-C30 and QLQ-OV28 questionnaires) were recorded in the trial at baseline and every following three months until end of treatment.

2.3. Outcomes

The CLIO/BGOG-ov10 study was set up to be a biomarker study. The primary objective was the assessment of HRD in circulating tumor DNA to predict response to OLA monotherapy. Unfortunately, our analysis to perform this HRD test on circulating tumor DNA failed due to insufficient DNA, making further analyses of the primary endpoint impossible. Here we report on the secondary clinical objectives i.e. the efficacy evaluation in patients with both PSOC and PROC disease treated with OLA monotherapy versus physician's choice CT. The following secondary endpoints were evaluated: objective response rate (ORR), clinical

benefit rate (CBR), duration of clinical benefit (DCB) for at least 12 weeks, progression-free survival (PFS) and overall survival (OS). ORR is defined as the number of patients with a best overall response of complete remission (CR) and partial remission (PR) at any time up to and including the defined analysis cut-off point divided by the number of randomized patients evaluable at 12 weeks. CBR and DCB considered the proportion of patients achieving a clinical benefit, i.e. a best overall response of stable disease (SD) or response at the first scan at 12 weeks. As a post-hoc exploratory analysis, the time to first subsequent therapy (TFST) was also recorded. When randomized to physician's choice CT, patients had the possibility to cross over to OLA monotherapy at progression.

2.4. Statistical analysis

For comparison of descriptive statistics, Fisher's exact test was used for categorical variables and one-way ANOVA for continuous variables. Binary endpoints (ORR and CBR) were compared between treatment groups using Fisher's exact test. Patients with missing response data due to clinical progression before second CT were counted as non-responders. Time-to-event endpoints (PFS, OS, DCB and TFST) were measured from study treatment initiation and the Kaplan-Meier method was used to calculate medians and accompanying 95%. The median follow-up time was calculated using the reverse Kaplan-Meier method [13]. We used R (version 3.6.1) for all statistical analysis. The trial was registered with ClinicalTrials.gov, NCT02822157.

3. Results

Between September 19, 2016 and February 4, 2019, 160 patients were randomized in a 2:1 fashion in two separate cohorts according to platinum sensitivity: 60 patients with PSOC and 100 patients with PROC (Fig. 1). Combined, 107 patients were randomized to OLA and 53 patients to physician's choice CT. After randomization, it was noted that one patient, randomized in the PSOC cohort, was actually platinum-resistant and received treatment with gemcitabine. This patient was further analyzed in the PSOC cohort (intention-to-treat population). At the time of database lock (December 1, 2020), three patients were still on initial treatment (all three patients randomized to OLA monotherapy). The median follow-up time was 34 months (95%CI: 30.8–42.1 months).

The median age for all patients ($n = 160$) was 63 years (IQR 57–70). Baseline characteristics were well balanced between randomized treatment groups (Table 1). The majority of histological diagnoses consisted of high-grade serous histology (91.9%), but also 11 patients with clear-cell histology (~7%) were included. No PSOC patients had known BRCA mutations at time of randomization. In PROC group 12 patients (12.0%) had *BRCA1* mutation and three (3.0%) *BRCA2* mutation at randomization. In PSOC, somatic testing during trial revealed five *BRCA1* mutations (8.3%) and one *BRCA2* mutation (1.7%). In PROC, one additional *BRCA1* mutation was revealed during the course of the trial. Patients randomized to OLA received a median of three prior lines of treatment (range 1–8) compared to a median of two prior lines of treatment in the CT arm (range 1–8). Eight patients (5%) received prior treatment with a PARP inhibitor and an additional nine patients (6%) were previously included in placebo-controlled randomized trials with PARP inhibitors. Over one third of patients (36%) received four or more lines of prior systemic therapy. Baseline characteristics according to inclusion cohort are shown in **S1** (Supplementary Table 1).

All 160 randomized patients had measurable disease at baseline and 145 patients (91%) of patients were evaluable for response (Fig. 1). Responses were observed in 26 (24.3%) of 107 participants in the OLA group versus 15 (28.3%) of 53 participants in the CT group ($p = 0.701$; Table 2). The proportion of patients with a clinical benefit (CBR, i.e., response and SD at 12 weeks) was 58 (54.2%) of 107 participants in the OLA group versus 30 (56.6%) of 53 participants in the CT group

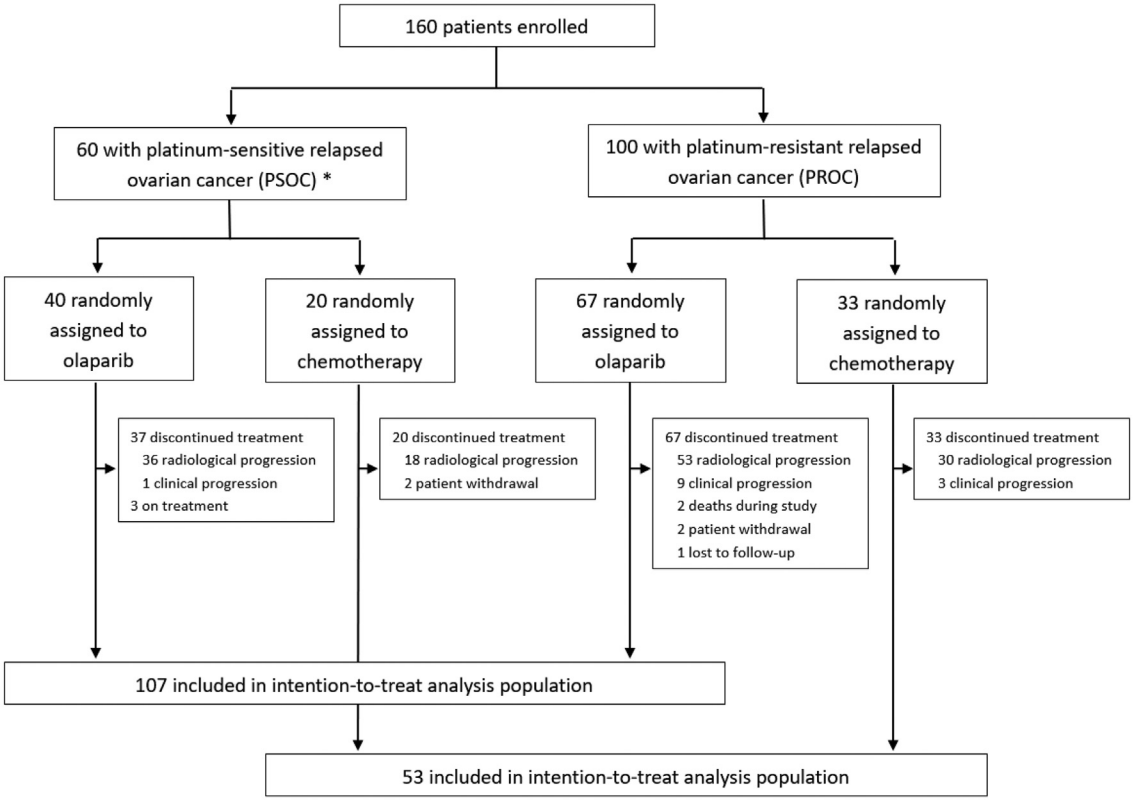

Fig. 1. CLIO trial profile (data cutoff December 1, 2020), * 1 PROC patient was randomized in PSOC cohort and received gemcitabine chemotherapy (evaluable, PR).

Table 1
Patient demographics and baseline characteristics.

		Olaparib monotherapy n = 107	Chemotherapy n = 53	*p*-value
Median age (IQR)		63 (57–70)	63 (59–70)	0.563
Age category (%)	18–70	77 (72.0)	38 (71.7)	1.000
	>70	30 (28.0)	15 (28.3)	
WHO-score (%)	0	59 (55.1)	30 (56.6)	1.000
	1	46 (43.0)	22 (41.5)	
	2	2 (1.9)	1 (1.9)	
Inclusion cohort	PROC	67 (62.6)	33 (62.3)	1.000
	PSOC	40 (37.4)	20 (37.7)	
Histology (%)	HGEOC	1 (0.9)	0 (0.0)	1.000
	HGSOC	98 (91.6)	49 (92.5)	
	MMMT	1 (0.9)	0 (0.0)	
	OCCC	7 (6.5)	4 (7.5)	
BRCA mutation[a] (%)	BRCA	18 (17.8)	4 (7.5)	0.144
	No BRCA	89 (83.1)	49 (92.5)	
BRCA mutation type[a] (%)	Germline BRCA1	12 (11.2)	2 (3.8)	-
	Germline BRCA2	3 (2.8)	0 (0.0)	
	Somatic BRCA1	2 (1.9)	2 (3.8)	
	Somatic BRCA2	1 (0.9)	0 (0.0)	
Previous bevacizumab (%)	Yes	57 (53.3)	24 (45.3)	0.402
	No	50 (46.7)	29 (54.7)	
Previous PARP inhibitor (%)	Yes	5 (4.7)	3 (5.7)	0.651
	No	97 (90.7)	46 (86.8)	
	Possible[b]	5 (4.7)	4 (7.5)	
Prior lines of systemic therapy (%)	1	19 (17.8)	10 (18.9)	0.775
	2	24 (22.4)	17 (32.1)	
	3	24 (22.4)	8 (15.1)	
	4	20 (18.7)	11 (20.8)	
	5	10 (9.3)	2 (3.8)	
	6	3 (2.8)	2 (3.8)	
	7	2 (1.9)	1 (1.9)	
	8	5 (4.7)	2 (3.8)	
Prior lines category (%)	3 or less	67 (62.6)	35 (66.0)	0.729
	4 or more	40 (37.4)	18 (34.0)	
Type of chemotherapy (%)	PLD	–	10 (18.9)	1.000
	Gemcitabine	–	7 (13.2)	
	Taxol	–	11 (20.8)	
	Topotecan	–	6 (11.3)	
	Carboplatin-PLD	–	5 (9.4)	
	Carboplatin-Gemcitabine	–	14 (26.4)	

IQR: interquartile range; WHO-score World Health Organization score; PSOC platinum sensitive ovarian cancer; PROC platinum resistant ovarian cancer; HGEOC: high grade endometrioid ovarian cancer; HGSOC: high grade serous ovarian cancer; MMMT: Malignant Mixed Mullerian tumor of the ovary; OCCC: clear cell ovarian cancer; PLD Pegylated Liposomal Doxorubicin.
[a] Including BRCA mutations discovered after randomization.
[b] Patients that were previously included in placebo-controlled randomized trials with PARP-inhibitors.

($p = 0.866$; Table 2). For the patients with PSOC disease, the ORR was 35.0% (14/40) for OLA versus 65.0% (13/20) for CT ($p = 0.053$); the CBR was 80.0% (32/40) for OLA versus 75.0% (15/20) for CT ($p = 0.744$). For the patients with PROC disease, the ORR was 17.9% (12/67) for OLA versus 6.1% (2/33) for CT ($p = 0.134$); the CBR was 38.8% (26/67) for OLA versus 45.5% (15/33) for CT ($p = 0.666$). Tumor responses according to platinum sensitivity and presence of BRCA mutation are visualized in the waterfall plot (Fig. 2**)**.

Patients with BRCA-mutated disease (either germline or somatic) had a response rate of 39% (7/18) for OLA versus 2 out of 4 for CT and a CBR of 67% (12/18) for OLA versus 4 out of 4 for CT. No significant differences in ORR or CBR were noted when stratifying for BRCA mutations in the PSOC and PROC cohorts separately (see **S2 -** Supplementary Table 2). As mentioned in the methods, PSOC patients with a known germline or somatic BRCA mutation at time of randomization were not eligible to participate in the study. As shown in **S1-**Supplementary Table 1, all PSOC patients had no known BRCA mutation before or at randomization. In enrolled patients who were not previously tested, we initiated genetic testing (consent to genetic testing was an inclusion criterion of the trial) and, in the PSOC cohort, we could identify six patients (10.0%) who carried germline or somatic BRCA1/2 mutations. Response rates to OLA tended to be higher in BRCA-mutated disease than in BRCA wild-type disease, although responses were also observed in the latter group. (PSOC: 50.0 versus 33.2%, $p = 0.507$; PROC: 35.7 versus 13.2%, $p = 0.051$ for BRCA-mutated versus BRCA-wildtype cases respectively). It should be noted that response rates for CT were poor in the PROC cohort (2/33; 6.3%), while 35.7% (5/14) of patients with BRCA-mutated PROC disease and 13.2% (7/53) of patients with BRCA-wild type PROC disease had a response with OLA (total response rate of 17.9% (12/67) for olaparib in PROC disease ($p = 0.134$) compared with CT).

ORR for OLA was similar in patients who received three or less prior lines of systemic therapy compared to patients who received four lines or more (25.4 versus 22.5% respectively, $p = 0.737$; **S3**-Supplementary Table 3). In patients who received chemotherapy, ORR was lower in the latter group (11.1% versus 37.1%; $p = 0.046$). In patients with PROC disease, treated with four or more prior lines of treatment, the ORR for olaparib was 22.9% (8/35), compared to 0.0% (0/14) for chemotherapy ($p = 0.040$).

Off note, we included 11 cases with clear-cell histology (7 randomized to OLA, 4 to CT) and one response was seen in both arms. In the OLA arm, three out of seven patients with clear-cell histology had a clinical benefit compared to one out of four in the CT arm. Furthermore, responses in PROC patients randomized to chemotherapy were only seen with paclitaxel ($n = 2$), no responses were seen with PLD, gemcitabine or topotecan.

Table 2
Objective response rate (ORR) and clinical benefit rate (CBR), excluding non-evaluable cases.

	All patients ($n = 160$)			PSOC ($n = 60$)			PROC ($n = 100$)		
	OLA ($n = 107$)	CT ($n = 53$)	p	OLA ($n = 40$)	CT ($n = 20$)	p	OLA ($n = 67$)	CT ($n = 33$)	p
ORR	26	15	0.701	14	13	0.053	12	2	0.134
n	(24.3)	(28.3)		(35.0)	(65.0)		(17.9)	(6.1)	
%									
CR	3	2	–	3	2	–	0	0	–
n	(2.8)	(3.8)		(7.5)	(10.0)		(0.0)	(0.0)	
%									
PR	23	13	–	11	11	–	12	2	–
n	(21.5)	(24.5)		(27.5)	(55.0)		(17.9)	(6.1)	
%									
SD	32	17	–	18	4	–	14	13	–
n	(29.9)	(32.1)		(45.0)	(20.0)		(20.9)	(39.4)	
%									
PD	38	17	–	7	2	–	31	15	–
n	(35.5)	(32.1)		(17.5)	(10.0)		(46.3)	(45.5)	
%									
NE	11	4	–	1	1	–	10	3	–
n	(10.3)	(7.5)		(2.5)	(5.0)		(14.9)	(9.1)	
%									
CBR	58	30	0.866	32	15	0.744	26	15	0.666
n	(54.2)	(56.6)		(80.0)	(75.0)		(38.8)	(45.5)	
%									

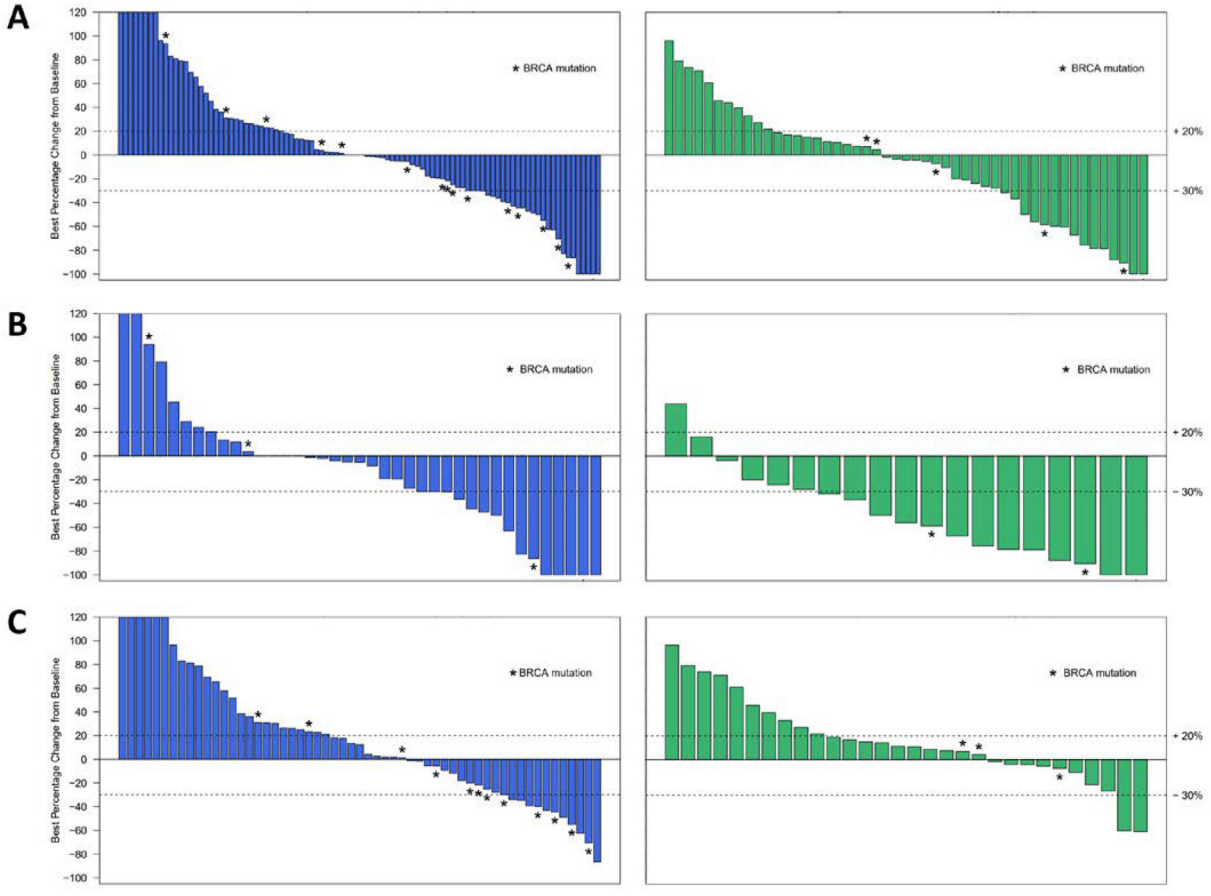

Fig. 2. Waterfall plots showing best response according to RECIST v1.1. for all evaluable patients (**A**, $n = 145$; 96 OLA, 49 CT), for patients with PSOC disease (**B**, $n = 58$; 39 OLA, 19 CT) and PROC disease (**C**, $n = 87$; 57 OLA, 30 OLA). Panels on the left represent patients on olaparib (in blue) and panels on the right represent patients on chemotherapy (in green). Each bar represents an evaluable patient. BRCA 1 and 2 mutations are annotated with (*).

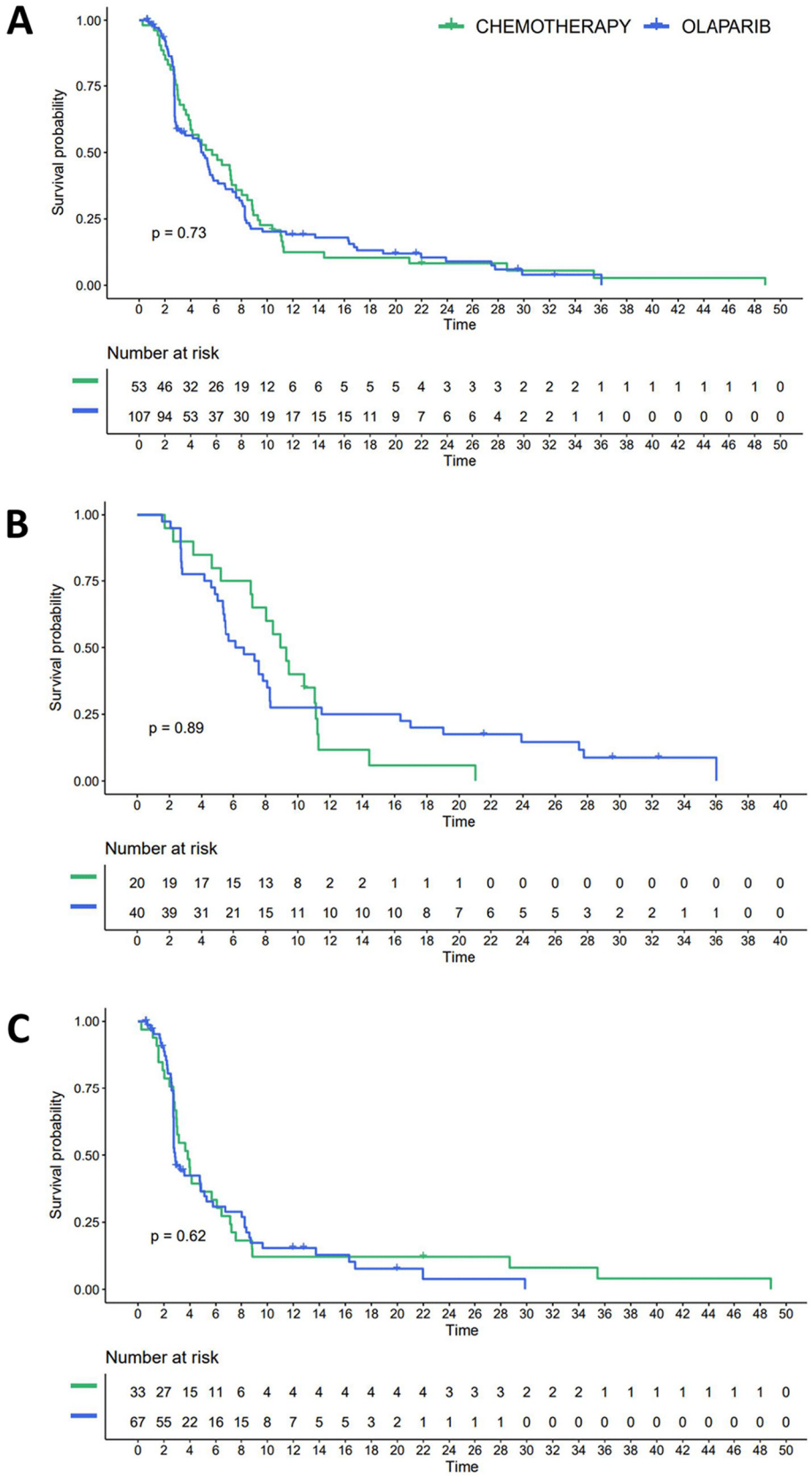

Fig. 3. Kaplan-Meier plots of PFS for all patients (**A**), for patients with PSOC disease (**B**) and for patients with PROC disease (**C**).

Median PFS was 4.8 months (95% CI 3.2–6.1) in the OLA group versus 5.7 months (95% CI 4.0–8.0) in the CT group (hazard ratio [HR] 1.07 [95% CI 0.66–1.32]; log-rank $p = 0.700$; Fig. 3A). For patients with PSOC disease, the median PFS was 6.4 months (95% CI 5.3–8.3) in the OLA group versus 9.1 months (95% CI 7.2–11.2) in the CT group (hazard ratio [HR] 0.96 [95% CI 0.54–1.72]; log-rank $p = 0.900$; Fig. 3B). For patients with PROC disease, the median PFS was 2.9 months (95% CI 2.8–5.1 in the OLA group versus 3.8 months (95% CI 3.0–6.4) in the CT group (hazard ratio [HR] 1.11 [95% CI 0.72–1.78]; log-rank $p = 0.600$; Fig. 3C).

Median OS at the time of data cutoff for the final analysis was 12.5 months (95% CI 9.0–17.2) in the OLA group versus 14.4 months (95% CI 11.2–24.0) in the CT group (hazard ratio [HR] 1.14 [95% CI 0.61–1.28]; log-rank $p = 0.500$, Fig. 4). For patients with PSOC disease, the median OS was 28.2 months (95% CI 20.2 - NA) in the OLA group versus 28.1 months (95% CI 19.6 – NA) in the CT group (hazard ratio [HR] 1.03 [95% CI 0.52–2.05]; log-rank p = 0.900; **S5-**Supplementary Fig. 1A). For patients with PROC disease, the median OS was 7.4 months (95% CI 5.9–12.0) in the OLA group versus 10.9 months (95% CI 7.5–16.2) in the CT group (hazard ratio [HR] 1.28 [95% CI 0.82–2.00]; log-rank $p = 0.3$; **S5-**Supplementary Fig. 1B).

Median DCB was 5.4 months (95% CI 3.7–6.0) in the OLA group versus 5.1 months (95% CI 3.9–7.5) in the CT group (hazard ratio [HR] 0.79 [95% CI 0.50–1.25]; log-rank $p = 0.300$; **S6-**Supplementary Fig. 2A). For patients with PSOC disease, the median DCB was 5.1 months (95% CI 3.4–13.8) in the OLA group versus 6.4 months (95% CI 5.1–11.9) in the CT group (hazard ratio [HR] 0.86 [95% CI 0.44–1.68]; log-rank $p = 0.700$; **S6-**Supplementary Fig. 2B). For patients with PROC disease, the median DCB was 5.5 months (95% CI 2.8–13.8) in the OLA group versus 3.8 months (95% CI 2.8–6.1) in the CT group (hazard ratio [HR] 0.79 [95% CI 0.40–1.56]; log-rank $p = 0.500$; **S6-**Supplementary Fig. 2C). Median TFST was 8.7 months (95% CI 6.8–9.9) in the OLA group versus 7.2 months (95% CI 5.5–9.0) in the CT group (hazard ratio [HR] 0.60 [95% CI 0.41–0.90]; log-rank $p = 0.010$; **S7-**Supplementary Fig. 3A). For patients with PSOC disease, the median TFST was 9.5 months (95% CI 7.2–17.4) in the OLA group versus 9.5 months (95% CI 8.6–11.3) in the CT group (hazard ratio [HR] 0.71 [95% CI 0.38–1.34]; log-rank p = 0.300; **S7-**Supplementary Fig. 3B). For patients with PROC disease, the median TFST therapy was 7.5 months (95% CI 5.9–10.0) in the OLA group versus 4.6 months (95% CI 3.2–7.6) in the CT group (hazard ratio [HR] 0.53 [95% CI 0.32–0.88]; log-rank p = 0.010; **S7-**Supplementary Fig. 3C).

Adverse event analysis showed no unexpected findings for the PARP inhibitor olaparib. The most common drug related side effects were nausea (51%), fatigue (50%) and vomiting (41%) [14]. The most common hematological toxicities were anemia (42%), neutropenia (5%) and thrombocytopenia (3%) (**S4**-Supplementary Table 4**).** Dose reduction was necessary in only 17% of patients treated with OLA; in 6% of patients, discontinuation of olaparib was necessary.

4. Discussion

In this report, we provide the first randomized data of PARP inhibitor monotherapy versus standard chemotherapy in patients without a BRCA mutation and relapsed OC. Our study showed overall an equal efficacy for OLA compared to standard CT. ORR for OLA in our study population (24.3% for all patients, 35.0% for patients with PSOC disease) was comparable with the results from single-arm trials with PARP inhibitor monotherapy for relapsed OC [6–8].

In the PSOC cohort, ORR tended to be lower for OLA but no significant difference was observed between OLA monotherapy compared to standard CT. PFS, OS, DCB, and TFST were similar in this population. The role of PARP inhibitors in BRCA mutated patients is already well described. The results of this trial broaden the scope to BRCA wild type patients in the advanced setting. In the BRCA wild-type group, we recorded a significant number of tumor responses to OLA. The treatment of relapsed OC remains challenging due to limited options. Our study showed similar progression-free and overall survival rates on OLA monotherapy compared to platinum-based chemotherapy in the PSOC cohort. In our opinion this opens the possibility for an extra treatment line in this clinically challenging relapsed setting. Due to the aforementioned inclusion criteria (i.e., exclusion of BRCA mutated cases known at time of inclusion), it should be noted that the frequency of BRCA mutation at final analysis in this cohort was lower than in other studies in PSOC.

In PROC, olaparib monotherapy resulted in a favorable objective response rate of 17.9% compared to 6.1% with standard chemotherapy. Known BRCA mutations were included in this cohort with a response rate of 38.9% for BRCA positive patients treated with OLA and a clinical

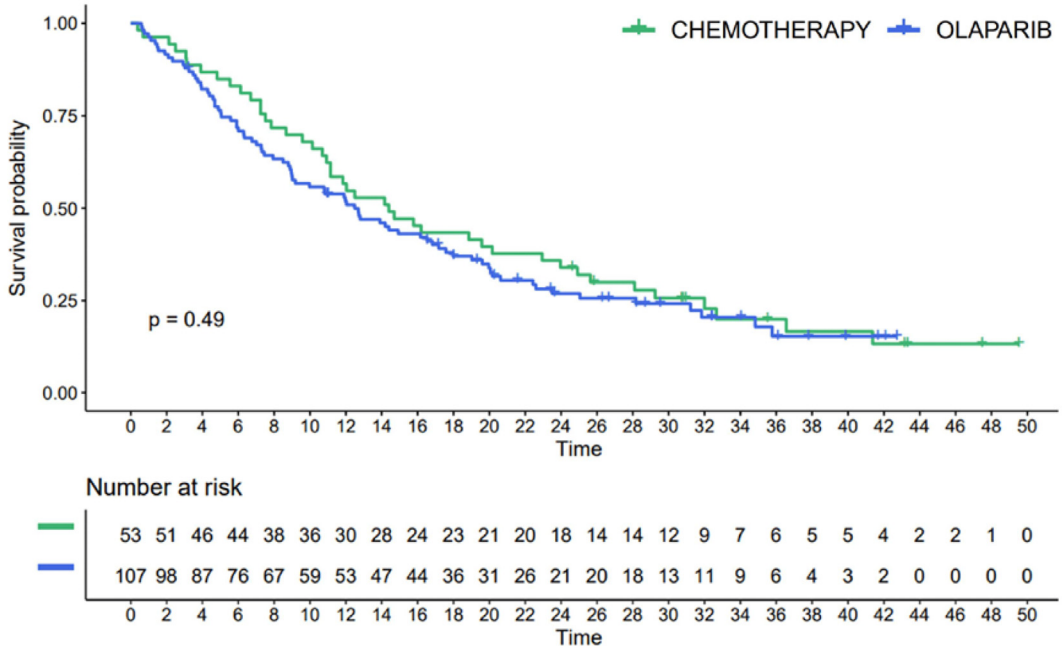

Fig. 4. Kaplan-Meier plots of overall survival for all patients receiving either olaparib or chemotherapy.

benefit rate of 66.7%. In heavily pretreated patients (four lines or more) with PROC disease, we observed a significant difference in response rate: 28.6% for olaparib versus no responses with CT. We observed a significant increase in TFST with OLA in patients with PROC disease compared to CT, however there were no significant differences in PFS, OS or DCB in the whole group, nor in cohorts according to platinum sensitivity.

No new adverse events were noted with olaparib treatment, the drug-related side effects profile was consistent with previous studies with OLA [14]. Strengths of our study are the randomized design and the inclusion of well-defined populations of patients with PROC and PSOC disease. However, the number of non-evaluable cases (15 patients 9.4%), mainly attributed to the fast progression in PROC patients, should be taken into account.

The CLIO clinical trial provides valuable information on the role of OLA as monotherapy in relapsed ovarian cancer comprising both, a platinum resistant and sensitive population in real-world setting. This PARP inhibitor therefore provides us with a relevant treatment option as an alternative for standard chemotherapy in a clinically challenging stage of the disease.

5. Conclusion

Olaparib single-agent therapy demonstrates encouraging efficacy compared with chemotherapy in a broad population of heavily pretreated relapsed OC compromising mainly platinum-resistant and germline BRCA1/2-wildtype disease.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.01.034.

Authors' contributions

Vanderstichele A., Loverix L., Vergote I., Lambrechts D., Van Nieuwenhuysen E.: Conception and design.

Vanderstichele A., Loverix L., Vergote I., Han S., Callewaert T., Olbrecht S., Van Gorp T: Collection and assembly of data.

Vanderstichele A., Loverix L., Vergote I., Busschaert P., Berteloot P., Neven P., Lambrechts D., Callewaert T., Van Gorp T.: Data analysis and interpretation.

Vanderstichele A., Loverix L., Vergote I., Van Nieuwenhuysen E., Han S., Concin N., Callewaert T., Van Gorp T.: Provision of study material or patients.

Vanderstichele A. and Loverix L. and Callewaert T.: Administrative support:

All authors except for Berteloot P., Neven P., Olbrecht S. and Lambrechts D.: Manuscript writing.

All authors approved the final manuscript.

Acknowledgments of research support:

- Astra Zeneca: drug supply

List of previous presentations:

- Vanderstichele A et al. Randomized phase II CLIO study on olaparib monotherapy versus chemotherapy in platinum-resistant ovarian cancer. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 5507–5507. (ASCO annual meeting 2019)
- Loverix L et al. Randomized phase II CLIO study on olaparib versus chemotherapy in platinum-sensitive recurrent ovarian cancer. Gynaecologic Oncology 159, supplement 1, 17–18 (October 01, 2020). (SGO annual meeting 2020)

Credit author statement

Vanderstichele A.: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing original draft, review & editing.

Loverix L.: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing original draft, review & editing.

Busschaert P.: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing review & editing.

Van Nieuwenhuysen A.: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing review & editing.

Han S.: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing review & editing.

Concin N.: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing review & editing.

Callewaert T.: Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing review & editing.

Olbrecht S.: Data curation, Investigation, Resources.

Salihi R.: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing review & editing.

Berteloot P.: Data curation, Investigation, Resources, Supervision, Validation, Writing review & editing.

Neven P.: Data curation, Formal analysis, Investigation, Resources, Supervision, Validation, Writing review & editing.

Lambrechts D.: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing review & editing.

Van Gorp T.: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing review & editing.

Vergote I.: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing original draft, review & editing.

Acknowledgments and funding

We want to thank the patients and their families. We thank Joke De Roover, Tine Op De Beeck, Ellen Reynders and their colleagues at our clinical trial unit for their contribution in trial design and execution. We thank Annick Van den Broeck for biological sample management. We thank Annouschka Laenen for the support in statistical analysis. We thank Astra Zeneca for the supply of olaparib. We thank Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, U.S.A."

The study was funded by 'Kom op Tegen Kanker' (Stand up to Cancer, the Flemish cancer society 2016/10728/2603) and by the 'Vriendtjes tegen Kanker' fund (grant number EVO-FOVTK1-O2010). Toon Van Gorp is a Senior Clinical Investigator of the Fund for Scientific Research-Flanders (FWO Vlaanderen 18B2921N). Liselore Loverix is predoctoral researcher of the Fund for Scientific Research-Flanders (FWO Vlaanderen 1S41921). The funders had no role in study design, data collection, analysis, interpretation or writing of the report.

Declaration of Competing Interest

Dr. Lambrechts reports personal fees from Astra Zeneca (Advisory boards and speaker's fee), personal fees from MSD (Advisory boards), grants from Agilent Technologies (industry-sponsored grant), outside the submitted work. In addition, Dr. Lambrechts has a patent application pending. **I. Vergote** reports grants and other from Amgen (Europe) GmbH (2019), personal fees and other from AstraZeneca

(2019–2022), other from Clovis Oncology Inc. (2019–2019), other from Carrick Therapeutics (2019), other from Deciphera Pharmaceuticals (2020—2021), personal fees from Elevar Therapeutics (2020), personal fees and other from F. Hoffmann-La Roche Ltd. (2019–2021), other from Genmab (2019–2021), personal fees and other from GSK (2019–2021), personal fees and other from Immunogen Inc. (2019–2022), personal fees from Jazzpharma (2021—2022), personal fees from Mersana (2020), other from Millennium Pharmaceuticals (2019), personal fees and other from MSD (2019–2022), personal fees and other from Novocure (2020—2022), personal fees from Octimet Oncology NV (2019), personal fees and other from Oncoinvent AS (2019–2022), personal fees and other from Sotio a.s. (2019–2022), personal fees from Verastem Oncology (2020), personal fees from Zentalis (2020), grants and other from Roche, other from Tesaro, personal fees from Agenus (2021), personal fees from Aksebio (2021), personal fees from Eisai (2021), personal fees from Karyopharm (2021), personal fees from Novartis (2021), personal fees from Seagen (2021), outside the submitted work. All other authors declared no conflicts of interest.

References

[1] C. Allemani, T. Matsuda, V. Di Carlo, et al., Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries, Lancet 391 (2018) 1023–1075.

[2] M. Timmermans, G.S. Sonke, K.K. Van de Vijver, et al., No improvement in long-term survival for epithelial ovarian cancer patients: a population-based study between 1989 and 2014 in the Netherlands, Eur. J. Cancer 88 (2018) 31–37.

[3] A. Vanderstichele, P. Busschaert, S. Olbrecht, et al., Genomic signatures as predictive biomarkers of homologous recombination deficiency in ovarian cancer, Eur. J. Cancer 86 (2017) 5–14.

[4] S. Lheureux, C. Gourley, I. Vergote, A.M. Oza, Epithelial ovarian cancer, Lancet 393 (10177) (2019) 1240–1253.

[5] N. Colombo, C. Sessa, A. Du Bois, et al., ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease, Ann. Oncol. 30 (5) (2019) 672–705.

[6] G. Kim, G. Ison, A.E. McKee, et al., FDA approval summary: Olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy, Clin. Cancer Res. 21 (19) (2015) 4257–4261.

[7] S. Balasubramaniam, J.A. Beaver, S. Horton, et al., FDA approval summary: Rucaparib for the treatment of patients with deleterious BRCA mutation–associated advanced ovarian cancer, Clin. Cancer Res. 23 (23) (2017) 7165–7170.

[8] K.N. Moore, A.A. Secord, M.A. Geller, et al., Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial, Lancet Oncol 20 (5) (2019) 636–648.

[9] L.T. Melinda, M.T. Kirsten, R. Julia, et al., Homologous recombination deficiency (hrd) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer, Clin. Cancer Res. 22 (15) (2016) 3764–3773.

[10] A. Du Bois, A. Reuss, E. Pujade-Lauraine, et al., European network of gynaecological oncological trial groups' requirements for trials between academic groups and industry partners - first update 2015, Int. J. Gynecol. Cancer 25 (7) (2015) 1328–1330.

[11] E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2009) 228–247.

[12] NCI, Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [Internet], https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm 2017.

[13] T.G. Clark, M.J. Bradburn, S.B. Love, et al., Survival analysis part IV: further concepts and methods in survival analysis, Br. J. Cancer 89 (5) (2003) 781–786.

[14] C.J. LaFargue, G.Z. Dal Molin, A.K. Sood, et al., Exploring and comparing adverse events between PARP inhibitors, Lancet Oncol 20 (1) (2019) e15–e28.