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Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial

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HIGHLIGHTS

- Patients with newly diagnosed, advanced ovarian cancer were classified by clinical risk and according to biomarker status.
- Higher risk: stage III with upfront surgery and residual disease or neoadjuvant chemotherapy, or stage IV.
- Lower risk: stage III with upfront surgery and no residual disease.
- Olaparib plus bevacizumab provided a progression-free survival benefit over bevacizumab in higher- and lower-risk patients.
- A substantial benefit was seen in higher- and lower-risk HRD-positive patients.

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ABSTRACT

Objectives. Adding maintenance olaparib to bevacizumab provided a significant progression-free survival (PFS) benefit in patients with newly diagnosed, advanced ovarian cancer in the randomized, double-blind PAOLA-1/ENGOT-ov25 trial (NCT02477644). We analyzed PFS by clinical risk and biomarker status.

Methods. Patients received olaparib 300 mg twice daily for up to 24 months plus bevacizumab 15 mg/kg every 3 weeks for up to 15 months in total, or placebo plus bevacizumab. This post hoc exploratory analysis evaluated PFS in patients classified as higher risk (stage III with upfront surgery and residual disease or neoadjuvant chemotherapy; stage IV) or lower risk (stage III with upfront surgery and no residual disease), and by biomarker status.

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Bevacizumab
Ovarian cancer
Newly diagnosed
Clinical risk

Results. Of 806 randomized patients, 74% were higher risk and 26% were lower risk. After a median 22.9 months of follow-up, PFS favored olaparib plus bevacizumab versus placebo plus bevacizumab in higher-risk patients (hazard ratio [HR] 0.60; 95% confidence interval [CI] 0.49–0.74) and lower-risk patients (0.46; 0.30–0.72). Olaparib plus bevacizumab provided a substantial PFS benefit versus bevacizumab alone in the homologous recombination deficiency (HRD)-positive subgroup (higher risk: HR 0.39; 95% CI 0.28–0.54 and lower risk: 0.15; 0.07–0.30), with 24-month PFS rates in lower-risk patients of 90% versus 43%, respectively (Kaplan–Meier estimates).

Conclusions. In PAOLA-1, maintenance olaparib plus bevacizumab provided a substantial PFS benefit in HRD-positive patients with a reduction of risk of progression or death of 61% in the higher-risk group and of 85% in the lower-risk group compared with bevacizumab alone.

1. Introduction

Patients with newly diagnosed, advanced ovarian cancer undergo cytoreductive surgery and platinum-based chemotherapy with curative intent. However, late diagnosis means that the majority of patients experience relapse [1]. Factors such as disease stage and the quality of surgical outcome impact their risk of relapse and survival, with improved progression-free survival (PFS) seen in patients with complete surgical resection, versus residual disease, after cytoreductive surgery [2].

The addition of the antiangiogenic agent bevacizumab to first-line treatment with carboplatin plus paclitaxel followed by maintenance bevacizumab prolonged PFS in the phase III GOG-0218 (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.63–0.82; $p < 0.001$) [3] and ICON7 (HR 0.81; 95% CI 0.70–0.94; $p = 0.004$) [4] trials in women with advanced ovarian cancer. An overall survival (OS) benefit was observed with post hoc analysis of patients with International Federation of Gynecology and Obstetrics (FIGO) stage IV disease in GOG-0218 (HR 0.75; 95% CI 0.59–0.95) [5] and higher-risk patients (stage III with residual disease following cytoreductive surgery [>1 cm], inoperable stage III disease, stage IV disease) in ICON7 (HR 0.78; 95% CI 0.63–0.97) [6].

Maintenance therapy with the poly(ADP–ribose) polymerase (PARP) inhibitor olaparib alone provided a substantial PFS benefit compared with placebo in patients with newly diagnosed, advanced ovarian cancer and a *BRCA1* and/or *BRCA2* mutation (BRCAm) in the phase III SOLO1 trial (HR 0.30; 95% CI 0.23–0.41; $P < 0.001$) [7]. Based on these results, maintenance olaparib is approved in the USA, the EU, China, Japan and other countries worldwide for women with a BRCAm [8–11].

The phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644) evaluated the addition of maintenance olaparib to bevacizumab in patients with newly diagnosed, advanced ovarian cancer who were candidates to receive bevacizumab in combination with first-line platinum-based chemotherapy and who were unselected by biomarker or surgical status [12]. Maintenance olaparib plus bevacizumab provided a significant PFS benefit compared with placebo plus bevacizumab in the overall PAOLA-1 population (median PFS 22.1 vs 16.6 months; HR 0.59; 95% CI 0.49–0.72; $P < 0.001$). In prespecified subgroup analyses, the greatest PFS benefit occurred with olaparib plus bevacizumab versus placebo plus bevacizumab in patients who tested positive for homologous recombination deficiency (HRD; defined as a BRCAm and/or genomic instability) (median PFS 37.2 vs 17.7 months; HR 0.33; 95% CI 0.25–0.45) and in patients with a tumor BRCAm (median PFS 37.2 vs 21.7 months; HR 0.31; 95% CI 0.20–0.47) [12]. Based on this result, maintenance olaparib plus bevacizumab was approved in the USA, the EU and Japan for HRD-positive patients with advanced ovarian cancer who are in response to first-line platinum-based chemotherapy plus bevacizumab [8,9,13].

Patient selection into PAOLA-1 was not restricted on the basis of surgical outcome, meaning that patients with stage III disease and no residual macroscopic disease following upfront cytoreductive surgery ('lower-risk' patients) were eligible for enrollment [12] as all patients with newly diagnosed, advanced ovarian cancer are at risk for disease progression and death, with approximately 70% of patients experiencing relapse within 3 years following primary treatment [1].

This article reports results of a post hoc exploratory subgroup analysis of PAOLA-1 evaluating combination therapy with olaparib plus bevacizumab versus placebo plus bevacizumab in patients considered at higher risk and lower risk for progression and by biomarker status.

2. Methods

2.1. Patients

Eligible patients had newly diagnosed, FIGO stage III or IV, high-grade serous, high-grade endometrioid ovarian, primary peritoneal and/or fallopian tube cancer, or other epithelial non-mucinous ovarian cancer with a germline BRCAm. Patients were eligible irrespective of surgical outcome and had no evidence of disease or clinical complete or partial response after first-line treatment with platinum-taxane chemotherapy plus bevacizumab. A tumor sample had to be available for central BRCA testing and to determine HRD status (supplementary material). Full eligibility criteria are provided in the supplementary material.

In this analysis, higher-risk patients were defined as those with FIGO stage III disease who had undergone upfront surgery and had residual disease or who had received neoadjuvant chemotherapy, or FIGO stage IV patients; this definition of higher risk was based on the disease stage and surgical status entry criteria used in the PRIMA/ENGOT-ov26 trial [14]. Lower-risk patients were those with FIGO stage III disease who had undergone upfront surgery and had complete resection.

2.2. Trial design and treatments

PAOLA-1/ENGOT-ov25 is a randomized, double-blind, multicenter, placebo-controlled phase III trial conducted in 11 countries. Randomization was performed centrally using a block design with stratification according to the outcome of first-line treatment at screening and tumor BRCAm status (supplementary material).

Patients were randomized, at least 3 weeks and no more than 9 weeks after the last dose of chemotherapy, in a 2:1 ratio to receive olaparib tablets 300 mg twice daily or placebo twice daily. Study treatment continued for up to 24 months or until investigator-assessed objective radiologic disease progression (modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) or unacceptable toxicity, whichever occurred first, as long as the patient experienced benefit and did not meet other discontinuation criteria. Following discontinuation of the study intervention, patients could receive other treatments at the investigators' discretion; crossover between the treatment arms was not planned.

All patients received intravenous bevacizumab 15 mg/kg every 3 weeks for a total duration of 15 months (including when administered in combination with chemotherapy).

2.3. Endpoints and assessments

The primary efficacy endpoint in PAOLA-1 (investigator-assessed PFS by modified RECIST version 1.1) has been reported previously [12]. Tumor assessment scans (computed tomography or magnetic resonance imaging) were performed at baseline and then every 24 weeks (or at 12-week planned visits if there was evidence of disease progression) up to month 42 or until the date of data cutoff.

This post hoc exploratory analysis evaluated investigator-assessed PFS in subgroups of patients considered higher risk and lower risk and according to biomarker profile. HRD positive was defined as a tumor BRCA mutation and/or a genomic instability score (GIS) of 42 or higher on the myChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA), HRD negative was defined as a GIS of less than 42 and HRD unknown was defined as an inconclusive, missing or failed test.

Safety and tolerability were evaluated as a secondary objective.

2.4. Trial oversight

This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, under the auspices of an independent data monitoring committee. The trial was designed by the European Network for Gynaecological Oncological Trial groups (ENGOT) lead group Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) and sponsored by Association de Recherche Cancers Gynecologiques (ARCAGY) Research, according to the ENGOT model A [15,16].

2.5. Statistical analysis

As previously reported [12], PAOLA-1 was powered to detect differences in investigator-assessed PFS (modified RECIST version 1.1) in the overall population.

All efficacy data were summarized and analyzed in the intent-to-treat (ITT) population (i.e. all randomized patients; full analysis set). Efficacy analyses used the electronic case report form data set, apart from the HRD analysis, for which Myriad data were used to determine HRD status.

Safety data were summarized in the safety analysis set (i.e. all randomized patients who received at least one dose of study treatment).

PFS was estimated using the Kaplan–Meier method. In the full analysis set, the stratified log-rank test assessed the difference between the treatment groups and the PFS HR and 95% CI were calculated using a stratified Cox proportional hazards model. For lower- and higher-risk patient subgroups, the HR and 95% CI were calculated from a single Cox proportional hazards model performed on the overall population, including a term for treatment, the subgroup covariate and the treatment by subgroup interaction term. The treatment effect HR was obtained for each level of the subgroup from this model. The Cox model was fitted with the Efron method to handle ties. For the BRCA-mutated and HRD subgroups, the same method mentioned above was applied on both the subpopulations of lower-risk and higher-risk patients.

Adverse events (AEs) were summarized descriptively.

3. Results

3.1. Patients

The median time from the first cycle of chemotherapy to randomization was 6 months (range 4–12). 806 patients underwent randomization (Supplementary Fig. S1). Of 595 patients in the higher-risk subgroup (74% of randomized patients), 398 of 399 patients in the olaparib plus bevacizumab arm and 194 of 196 patients in the placebo plus bevacizumab arm received study treatment. Of 211 patients in the lower-risk subgroup (26% of randomized patients), 137 of 138 patients in the olaparib plus bevacizumab arm and all 73 patients in the placebo plus bevacizumab arm received study treatment.

Patient baseline characteristics in the higher-risk and lower-risk subgroups, including BRCAm and HRD status, are shown in Table 1. Baseline characteristics were balanced between treatment arms in both subgroups. Numerically more patients in the lower-risk subgroup than in the higher risk subgroup had a tumor BRCAm (35% vs 28%) or were HRD-positive (57% vs 45%), although within each subgroup this remained balanced between the treatment arms.

3.2. Efficacy

Overall, the median (interquartile range [IQR]) follow-up for PFS was 22.9 (18.1–27.7) months (supplementary material). At primary analysis data cutoff (March 22, 2019), PFS events had occurred in 393 of 595 higher-risk patients (data maturity, 66%) and in 81 of 211 lower-risk patients (data maturity, 38%).

In the higher-risk subgroup, the HR for PFS for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.60 (95% CI 0.49–0.74); median PFS was 20.3 versus 14.7 months, respectively, and 37% versus 21% of patients, respectively, were free from disease progression and death at 24 months (Kaplan–Meier estimates) (Fig. 1A and Table 2). In the lower-risk subgroup, the HR for PFS for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.46 (95% CI 0.30–0.72); median PFS was unstable in the olaparib plus bevacizumab group due to lack of events and 73% of olaparib plus bevacizumab patients versus 46% of placebo plus bevacizumab patients were free from disease progression and death at 24 months (Kaplan–Meier estimates) (Fig. 1B and Table 2).

In higher-risk patients with a tumor BRCAm or who were HRD-positive, median PFS was unstable in the olaparib plus bevacizumab group due to lack of events. In patients with a tumor BRCAm, the HR for PFS for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.37 (95% CI 0.23–0.59) and 68% versus 37% of patients, respectively, were free from disease progression and death at 24 months (Kaplan–Meier estimates) (Table 2 and Fig. 1C). In HRD-positive patients, the HR for PFS for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.39 (95% CI 0.28–0.54) and 56% versus 23% of patients, respectively, were free from disease progression and death at 24 months (Kaplan–Meier estimates) (Table 2 and Fig. 1E). In higher-risk HRD-negative patients, the HR for PFS for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.93 (95% CI 0.68–1.30); median PFS was 15.6 versus 13.8 months, respectively, and 36% of patients in both treatment arms were free from disease progression and death at 24 months (Kaplan–Meier estimates) (Table 2 and Supplementary Fig. S2D).

Median PFS was not reached in lower-risk patients in the olaparib plus bevacizumab group who had a tumor BRCAm or were HRD-positive. In patients with a tumor BRCAm, the HR for PFS for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.11 (95% CI 0.03–0.31), with 96% versus 44% of patients, respectively, free from disease progression and death at 24 months (Kaplan–Meier estimates) (Table 2 and Fig. 1D). In HRD-positive patients, the HR for PFS for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.15 (95% CI 0.07–0.30), with 90% versus 43% of patients, respectively, free from disease progression and death at 24 months (Kaplan–Meier estimates) (Table 2 and Fig. 1F). No PFS benefit was seen in lower-risk HRD-negative patients receiving olaparib plus bevacizumab versus bevacizumab alone (Table 2 and Supplementary Fig. S3D).

PFS in other biomarker subgroups is shown in Table 2 (see also Supplementary Figs. S2, S3 and S4).

3.3. Safety

In higher-risk patients, the median (range) duration of treatment was 16.6 (0–33.0) months for olaparib and 13.4 (0.1–24.9) months for

Table 1
Characteristics of the patients at baseline[a].

	Overall population		Higher-risk subgroup[b]		Lower-risk subgroup[c]	
	Olaparib + bevacizumab (*N* = 537)	Placebo + bevacizumab (*N* = 269)	Olaparib + bevacizumab (*N* = 399)	Placebo + bevacizumab (*N* = 196)	Olaparib + bevacizumab (*N* = 138)	Placebo + bevacizumab (*N* = 73)
Median (range) age, years	61.0 (32.0–87.0)	60.0 (26.0–85.0)	62.0 (32.0–87.0)	61.0 (26.0–85.0)	59.0 (38.0–78.0)	56.0 (35.0–77.0)
ECOG performance status, n (%)						
0	378 (70)	189 (70)	275 (69)	134 (68)	103 (75)	55 (75)
1	153 (28)	76 (28)	119 (30)	59 (30)	34 (25)	17 (23)
Missing	6 (1)	4 (1)	5 (1)	3 (2)	1 (1)	1 (1)
Primary tumor location, n (%)						
Ovary	456 (85)	238 (88)	337 (84)	171 (87)	119 (86)	67 (92)
Fallopian tubes	39 (7)	11 (4)	25 (6)	7 (4)	14 (10)	4 (5)
Primary peritoneal	42 (8)	20 (7)	37 (9)	18 (9)	5 (4)	2 (3)
FIGO stage, n (%)						
III	378 (70)	186 (69)	240 (60)	113 (58)	138 (100)	73 (100)
IV	159 (30)	83 (31)	159 (40)	83 (42)	0 (0)	0 (0)
Histology, n (%)						
Serous	519 (97)	253 (94)	387 (97)	189 (96)	132 (96)	64 (88)
Endometrioid	12 (2)	8 (3)	8 (2)	4 (2)	4 (3)	4 (5)
Other[d]	6 (1)	8 (3)	4 (1)	3 (2)	2 (1)	5 (7)
History of cytoreductive surgery, n (%)						
Upfront surgery	271 (50)	138 (51)	133 (33)	65 (33)	138 (100)	73 (100)
Macroscopic residual disease	111 (41)	53 (38)	111 (83)	53 (82)	–	–
Complete resection	160 (59)	85 (62)	22[e] (17)	12[e] (18)	138 (100)	73 (100)
Interval surgery	228 (42)	110 (41)	228 (57)	110 (56)	0	0
Macroscopic residual disease	65 (29)	35 (32)	65 (29)	35 (32)	–	–
Complete resection	163 (71)	75 (68)	163 (71)	75 (68)	–	–
No surgery	38 (7)	21 (8)	38 (10)	21 (11)	0	0
Response after first-line therapy, n (%)						
NED[f]	290 (54)	141 (52)	153 (38)	70 (36)	137 (99)	71 (97)
Clinical CR[g]	106 (20)	53 (20)	106 (27)	53 (27)	–	–
Clinical PR[h]	141 (26)	75 (28)	140 (35)	73 (37)	1 (1)[i]	2 (3)[i]
Normal serum CA-125 level						
Yes	463 (86)	234 (87)	333 (83)	165 (84)	130 (94)	69 (95)
No	74 (14)	34 (13)	66 (17)	30 (15)	8 (6)	4 (5)
Missing	0	1 (<1)	0	1 (1)	0	0
Deleterious tumor BRCA mutation, n (%)[j]						
Yes	157 (29)	80 (30)	109 (27)	55 (28)	48 (35)	25 (34)
No	380 (71)	189 (70)	290 (73)	141 (72)	90 (65)	48 (66)
Myriad tumor HRD status,[k] n (%)						
HRD positive	255 (47)	132 (49)	177 (44)	89 (45)	78 (57)	43 (59)
HRD negative/unknown	282 (53)	137 (51)	222 (56)	107 (55)	60 (43)	30 (41)
HRD negative	192 (36)	85 (32)	144 (36)	62 (32)	48 (35)	23 (32)
Unknown	90 (17)	52 (19)	78 (20)	45 (23)	12 (9)	7 (10)

CA-125, cancer antigen 125; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; NED, no evidence of disease; PR, partial response.

[a] Percentages may not total 100 because of rounding.

[b] Patients with FIGO stage III disease who had undergone upfront surgery and had residual disease or who had received neoadjuvant chemotherapy, or FIGO stage IV patients.

[c] Patients with FIGO stage III disease who had undergone upfront surgery and had complete resection.

[d] In the overall ITT population, other defined as clear-cell ($n = 2$, olaparib plus bevacizumab), undifferentiated ($n = 1$, olaparib plus bevacizumab; $n = 6$, placebo plus bevacizumab) or other ($n = 3$, olaparib plus bevacizumab; $n = 2$, placebo plus bevacizumab). In the higher-risk subgroup, other defined as clear-cell ($n = 2$, olaparib plus bevacizumab), undifferentiated ($n = 1$, olaparib plus bevacizumab; $n = 2$, placebo plus bevacizumab) or other ($n = 1$, olaparib plus bevacizumab; $n = 1$, placebo plus bevacizumab). In the lower-risk subgroup, other defined as undifferentiated ($n = 4$, placebo plus bevacizumab) or other ($n = 2$, olaparib plus bevacizumab; $n = 1$, placebo plus bevacizumab).

[e] Patients with FIGO stage IV disease.

[f] No evidence of disease defined as no measurable or assessable disease after cytoreductive surgery plus no radiologic evidence of disease and a normal CA-125 level after chemotherapy.

[g] Clinical CR defined as the disappearance of all measurable or assessable disease and normalization of CA-125 levels after chemotherapy.

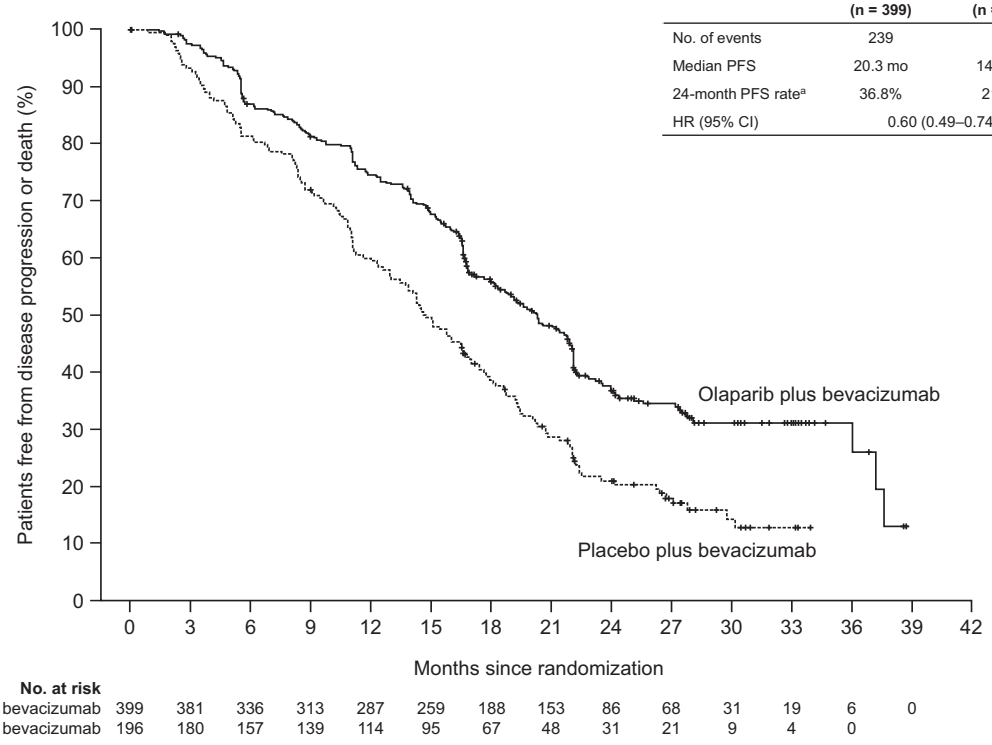
[h] Clinical PR defined as radiologic evidence of disease, an abnormal CA-125 level or both.

[i] No residual disease was reported at the time of surgery; however, computed tomography images compatible with residual disease were reported at postsurgical radiographic evaluation.

[j] As per the electronic case report form.

[k] HRD positive defined as a tumor BRCA mutation and/or a genomic instability score of 42 or higher on the myChoice® HRD Plus assay. HRD negative was defined as a genomic instability score of less than 42. "Unknown" was defined as an inconclusive, missing or failed test.

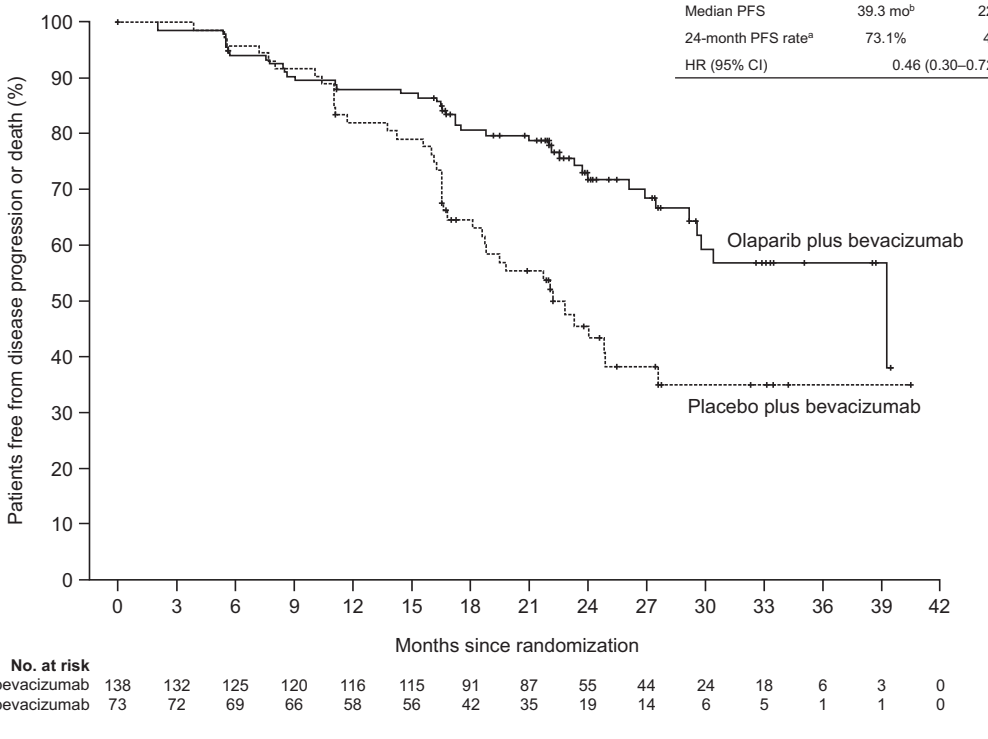
A



	Olaparib plus bevacizumab (n = 399)	Placebo plus bevacizumab (n = 196)
No. of events	239	154
Median PFS	20.3 mo	14.7 mo
24-month PFS rate[a]	36.8%	21.0%
HR (95% CI)	0.60 (0.49–0.74)	

No. at risk														
Olaparib plus bevacizumab	399	381	336	313	287	259	188	153	86	68	31	19	6	0
Placebo plus bevacizumab	196	180	157	139	114	95	67	48	31	21	9	4	0	

B

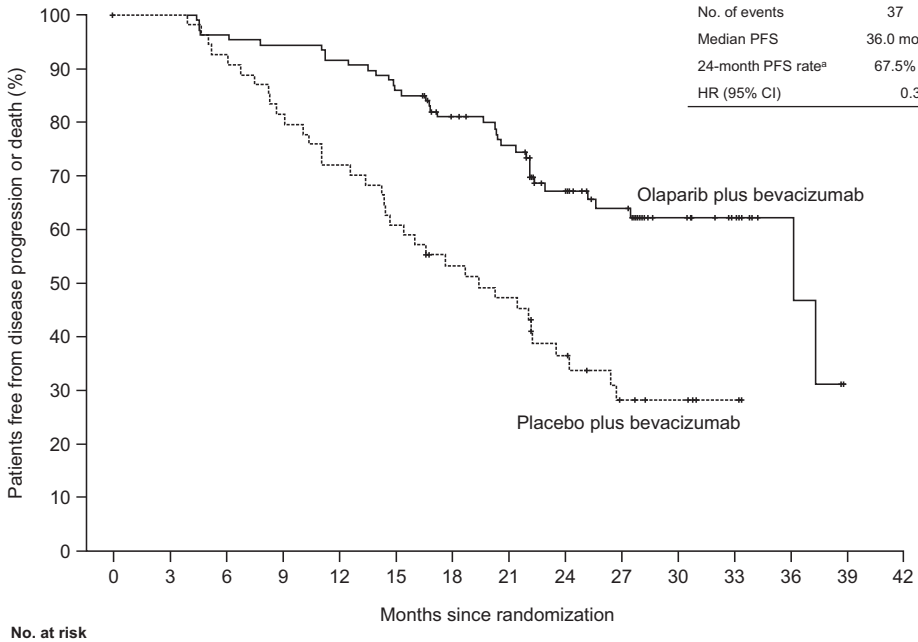


	Olaparib plus bevacizumab (n = 138)	Placebo plus bevacizumab (n = 73)
No. of events	41	40
Median PFS	39.3 mo[b]	22.9 mo
24-month PFS rate[a]	73.1%	45.6%
HR (95% CI)	0.46 (0.30–0.72)	

No. at risk														
Olaparib plus bevacizumab	138	132	125	120	116	115	91	87	55	44	24	18	6	3	0
Placebo plus bevacizumab	73	72	69	66	58	56	42	35	19	14	6	5	1	1	0

Fig. 1. Kaplan–Meier estimate of progression-free survival in the (A) higher-risk and (B) lower-risk subgroups, and (C) higher-risk patients with a tumor BRCA mutation, (D) lower-risk patients with a tumor BRCA mutation, (E) higher-risk HRD-positive patients and (F) lower-risk HRD-positive patients.
CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.
[a]Kaplan-Meier estimates.
[b]Unstable median due to lack of events.

C

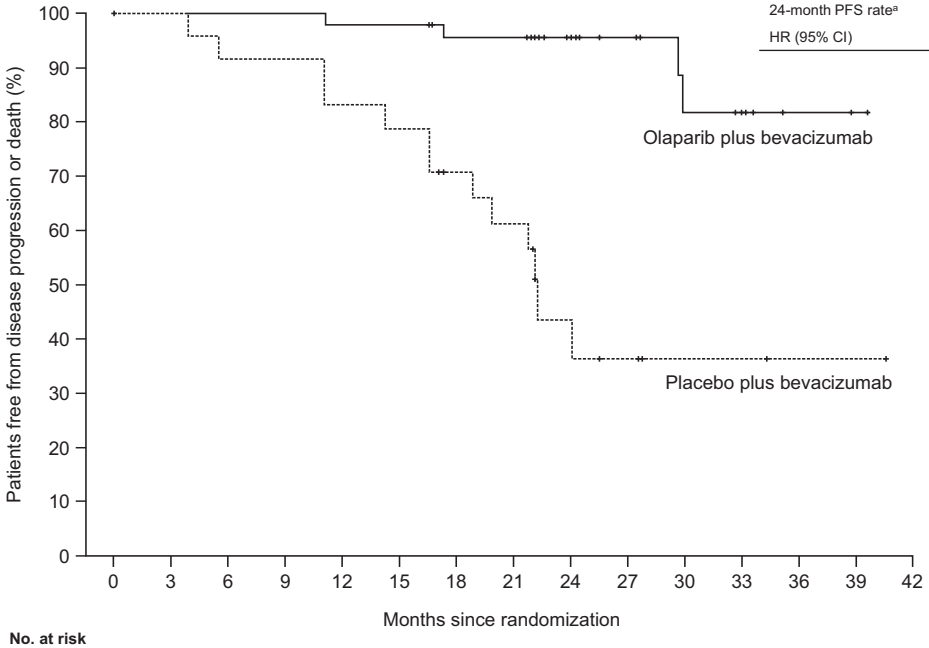


	Olaparib plus bevacizumab (n = 109)	Placebo plus bevacizumab (n = 55)
No. of events	37	36
Median PFS	36.0 mo[b]	19.4 mo
24-month PFS rate[a]	67.5%	36.5%
HR (95% CI)	0.37 (0.23–0.59)	

No. at risk

Olaparib plus bevacizumab	109	107	103	101	98	92	77	70	51	38	19	11	4	0
Placebo plus bevacizumab	55	54	50	44	39	33	26	23	16	9	5	2	0	

D



	Olaparib plus bevacizumab (n = 48)	Placebo plus bevacizumab (n = 25)
No. of events	4	13
Median PFS	NR	22.2 mo
24-month PFS rate[a]	95.5%	43.7%
HR (95% CI)	0.11 (0.03–0.31)	

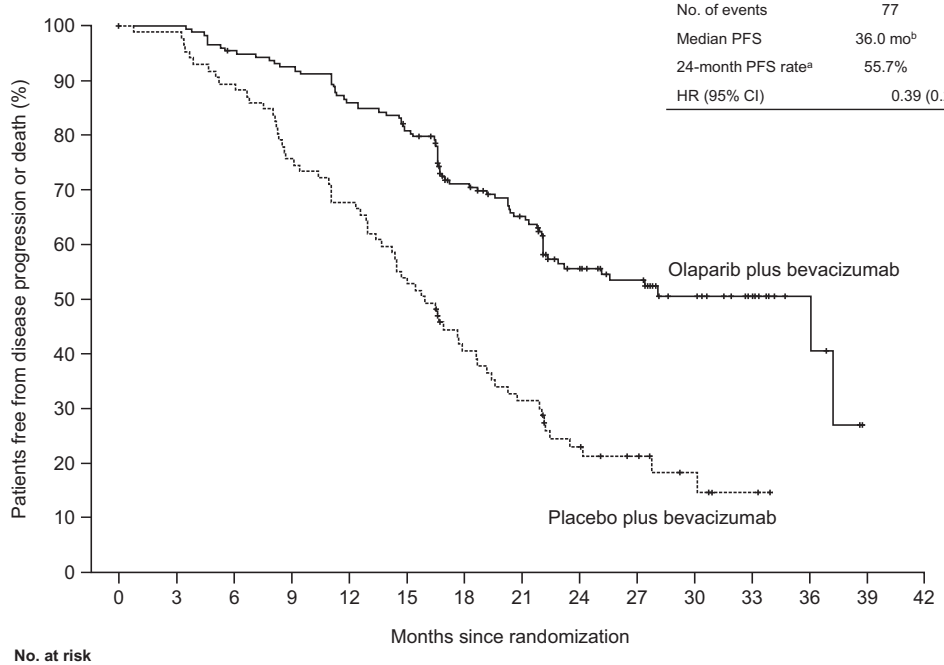
No. at risk

Olaparib plus bevacizumab	48	47	47	47	46	46	40	40	25	20	12	8	3	1	0
Placebo plus bevacizumab	25	24	22	22	20	19	15	13	6	4	2	2	1	1	0

Fig. 1 (*continued*).

E

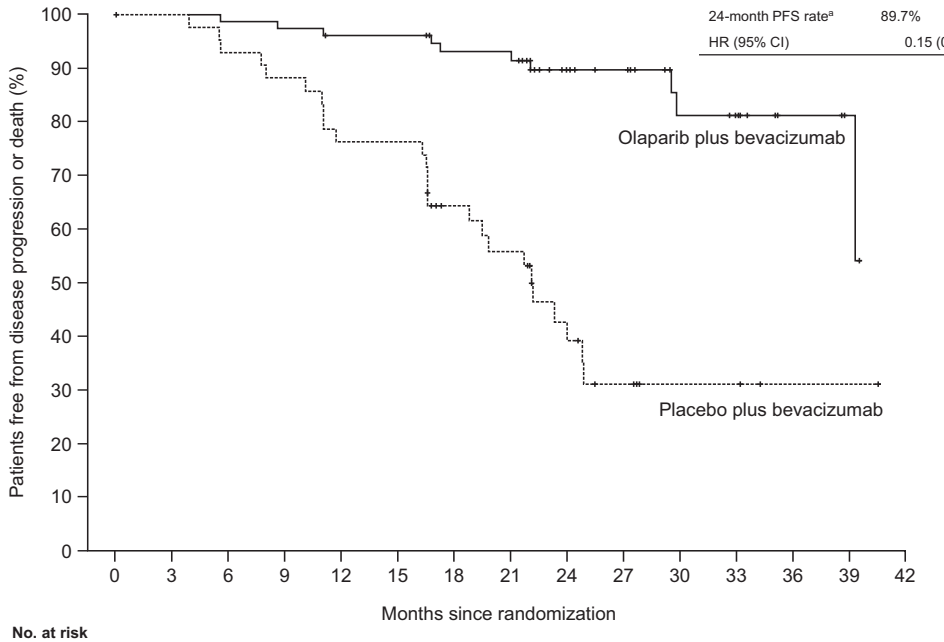
	Olaparib plus bevacizumab (n = 177)	Placebo plus bevacizumab (n = 89)
No. of events	77	67
Median PFS	36.0 mo[b]	16.0 mo
24-month PFS rate[a]	55.7%	23.1%
HR (95% CI)	0.39 (0.28–0.54)	



No. at risk														
Olaparib plus bevacizumab	177	175	166	161	150	140	109	95	63	50	27	15	5	0
Placebo plus bevacizumab	89	86	78	66	59	47	31	24	16	11	5	2	0	

F

	Olaparib plus bevacizumab (n = 78)	Placebo plus bevacizumab (n = 43)
No. of events	10	25
Median PFS	NR	22.1 mo
24-month PFS rate[a]	89.7%	42.6%
HR (95% CI)	0.15 (0.07–0.30)	



No. at risk														
Olaparib plus bevacizumab	78	77	76	75	73	73	60	60	40	35	19	14	6	3	0
Placebo plus bevacizumab	43	42	39	37	32	32	23	20	12	7	3	3	1	1	0

Fig. 1 (*continued*).

placebo, with a median (range) duration of treatment with bevacizumab since randomization of 11.0 (0.7–19.0) months in the olaparib group and 10.6 (0.7–17.1) months in the placebo group.

In lower-risk patients, the median (range) duration of treatment was 22.6 (0.1–25.5) months for olaparib and 19.8 (0.1–26.2) months for placebo, with a median (range) duration of treatment with

Table 2
Progression-free survival in higher-risk and lower-risk patients according to tumor biomarker status.

	Higher risk		Lower risk	
	Olaparib plus bevacizumab	Placebo plus bevacizumab	Olaparib plus bevacizumab	Placebo plus bevacizumab
ITT population	$n = 399$	$n = 196$	$n = 138$	$n = 73$
Median PFS, months	20.3	14.7	39.3[a]	22.9
HR (95% CI)	**0.60 (0.49–0.74)**		**0.46 (0.30–0.72)**	
Tumor BRCA mutation	$n = 109$	$n = 55$	$n = 48$	$n = 25$
Median PFS, months	36.0[a]	19.4	NR	22.2
HR (95% CI)	**0.37 (0.23–0.59)**		**0.11 (0.03–0.31)**	
No tumor BRCA mutation	$n = 290$	$n = 141$	$n = 90$	$n = 48$
Median PFS, months	16.7	13.8	29.2	22.9
HR (95% CI)	**0.68 (0.54–0.85)**		**0.69 (0.42–1.14)**	
HRD positive	$n = 177$	$n = 89$	$n = 78$	$n = 43$
Median PFS, months	36.0[a]	16.0	NR	22.1
HR (95% CI)	**0.39 (0.28–0.54)**		**0.15 (0.07–0.30)**	
HRD positive excluding a BRCA mutation[b]	$n = 64$	$n = 37$	$n = 33$	$n = 18$
Median PFS, months	20.3	15.4	39.3[a]	23.4
HR (95% CI)	**0.51 (0.31–0.83)**		**0.19 (0.06–0.55)**	
HRD negative/unknown	$n = 222$	$n = 107$	$n = 60$	$n = 30$
Median PFS, months	16.6	13.9	23.8	22.9
HR (95% CI)	**0.83 (0.64–1.08)**		**1.18 (0.65–2.25)**	
HRD negative	$n = 144$	$n = 62$	$n = 48$	$n = 23$
Median PFS, months	15.6	13.8	23.3	22.9
HR (95% CI)	**0.93 (0.68–1.30)**		**1.03 (0.54–2.06)**	
HRD unknown	$n = 78$	$n = 45$	$n = 12$	$n = 7$
Median PFS, months	19.8	14.3	NR	NR
HR (95% CI)	**0.63 (0.41–1.00)**		–[c]	

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.
[a] Unstable median due to lack of events.
[b] Patients without a BRCA mutation but with a genomic instability score of 42 or higher on the myChoice® HRD Plus assay.
[c] HR not reported because of the small number of patients in this subgroup.

bevacizumab since randomization of 11.0 (1.4–21.4) months in the olaparib group and 10.6 (0.7–16.1) months in the placebo group.

The tolerability profile of olaparib plus bevacizumab versus placebo plus bevacizumab was generally consistent across the higher-risk and lower-risk subgroups as well as being consistent with that reported in the overall PAOLA-1 population [12]. The most common AEs (all grades) and most common grade ≥3 AEs are reported in Supplementary Table S1.

Serious AEs occurred in 32% of olaparib plus bevacizumab patients and 31% of placebo plus bevacizumab patients in the higher-risk group, and in 30% versus 32%, respectively, in the lower-risk group. AEs with a fatal outcome occurred in 1 (0.3%) patient receiving olaparib plus bevacizumab and 2 (1%) patients receiving placebo plus bevacizumab in the higher-risk group, and in 0 versus 2 (3%) patients, respectively, in the lower-risk group.

The incidences of dose interruption and dose reduction because of AEs are shown in Supplementary Table S1. Discontinuation of olaparib or placebo because of AEs occurred in 19% of olaparib plus bevacizumab patients and 6% of placebo plus bevacizumab patients in the higher-risk group, and in 25% versus 5% of patients, respectively, in the lower-risk group (Supplementary Table S1).

4. Discussion

Even in advanced ovarian cancer, a disease setting where all patients are at high risk of progression, the goal of first-line treatment remains cure. The phase III PAOLA-1/ENGOT-ov25 trial included patients irrespective of risk status and maintenance olaparib plus bevacizumab improved PFS over placebo plus bevacizumab in both higher-risk and lower-risk patients. Consistent with the overall PAOLA-1 population [12], maintenance olaparib plus bevacizumab provided the greatest PFS benefit over placebo plus bevacizumab in higher-risk and lower-risk patients who had a tumor BRCAm or were HRD positive, highlighting the importance of HRD testing to identify patients most likely to benefit from and eligible to receive olaparib plus bevacizumab as maintenance therapy. It is important to note that lower-risk patients in the placebo plus bevacizumab arm of PAOLA-1 were still at high risk of progression, with over 50% experiencing progression or death at 24 months despite receiving standard treatment. This emphasizes the need to provide optimal treatment to all patients with newly diagnosed, advanced ovarian cancer regardless of disease stage or surgical status.

Another key element for improved prognosis remains surgical outcome [2]. Surgical outcome could be improved by surgical training/specialization [17–19] and may depend not only on training, but also on the preferences of clinicians and surgical centers [20].

The separation of the Kaplan–Meier curves occurred later in the lower-risk subgroup (at around 11 months) than in the higher-risk subgroup (at around 3 months) which could be explained by the underlying risk profile. After niraparib demonstrated a substantial effect on PFS in the phase III PRIMA/ENGOT-ov26 trial [14], which included only patients defined in our trial as higher risk, we expected to see the main difference in the corresponding cohort in PAOLA-1. Although the effect was consistent in both groups, we saw a greater PFS benefit with olaparib plus bevacizumab versus placebo plus bevacizumab in the lower-risk population than in the higher-risk population. It is unclear why the largest effect was seen in lower-risk patients. Hypotheses related to the underlying pathophysiology include: removal of poorly vascularized tumor with elimination of pharmacological sanctuaries; higher growth fraction in better perfused, small residual tumor masses, favoring increased cell kill with cytotoxic therapy; less opportunity for induced drug resistance with small tumor masses requiring fewer chemotherapy cycles; and enhanced host immunocompetence following removal of large tumor bulk [21]. A similar phenomenon was reported in patients with complete resection in the AGO-OVAR 12 trial [22] and following interval surgery in the VELIA trial [23].

Bevacizumab may not be offered to all lower-risk patients in routine clinical practice, despite data showing benefit in this subgroup of patients [24], and a randomized trial would be needed to definitively establish if maintenance therapy with a PARP inhibitor plus bevacizumab is more effective than maintenance therapy with a PARP inhibitor alone in these patients. The ongoing NIRVANA/ENGOT-ov63 trial [25] has the potential to confirm the benefit of bevacizumab in this group of patients

with no residual disease following upfront surgery. In our exploratory analysis in lower-risk PAOLA-1 patients, median PFS in the control arm was similar (approximately 22–23 months) across all biomarker subgroups, including those with a BRCAm, indicating that biomarker status did not significantly impact the PFS benefit provided by bevacizumab alone, as suggested by the results of retrospective subgroup analysis in the phase III GOG-0218 trial [26]. The substantial PFS benefit provided by olaparib plus bevacizumab in lower-risk patients with a tumor BRCAm or who were HRD positive, with 2-year PFS rates of ≥90%, raises the hope of long-term benefit or even cure in the newly diagnosed setting. Longer-term follow-up and final OS data are needed to establish the long-term benefit provided by olaparib plus bevacizumab in these PAOLA-1 patients.

As PAOLA-1 did not include a non-bevacizumab arm, the role of bevacizumab can currently only be explored indirectly by considering the results of other key trials [3,14] (Table S2). For patients with residual disease, the phase III PRIMA/ENGOT-ov26 trial of niraparib maintenance monotherapy enrolling higher-risk patients with newly diagnosed, advanced ovarian cancer who had an excellent response to platinum-based chemotherapy resulting in normalization or a 90% reduction in serum CA-125 levels during first-line therapy provided data [14]. Comparisons between results in the higher-risk subgroup from PAOLA-1 and the PRIMA trial [14] should be made with caution given differences between the trials in study design (e.g. PAOLA-1 had an active comparator arm whereas PRIMA had a placebo comparator arm) and baseline characteristics. However, only randomized trials dedicated to evaluating the role of PARP inhibitors with or without bevacizumab can provide definitive answers. One such trial is due to start shortly (AGO-OVAR 28/ENGOT-ov57; NCT05009082).

Whereas maintenance niraparib provided a PFS benefit compared with placebo in HRD-negative patients in PRIMA [14], our data indicate that the addition of a PARP inhibitor to bevacizumab did not provide a benefit in lower- or higher-risk HRD-negative patients. It is worth noting that the PRIMA population is more likely to be enriched for platinum response, a known biomarker of PARP inhibitor sensitivity, than the PAOLA-1 population. Data reporting OS and the impact of subsequent therapy are awaited with interest in HRD-negative patients, a group with high unmet need who require innovative therapies.

The tolerability profile of maintenance olaparib plus bevacizumab was as expected in the higher-risk and lower-risk populations and is consistent with the tolerability profile in the overall PAOLA-1 population [12]. Slightly more olaparib discontinuations were seen in lower-risk than in higher-risk patients in the olaparib plus bevacizumab arm, possibly reflecting the longer duration of treatment in lower-risk patients (median 22.6 vs 16.6 months in higher-risk patients).

Limitations of this analysis include its post hoc exploratory nature and the small number of patients in some of the biomarker subgroups.

Given the benefits shown with combination therapy in PAOLA-1, results of phase III trials evaluating the efficacy of triplet therapy including PARP inhibitors, antiangiogenic agents and immune checkpoint inhibitors in women with newly diagnosed advanced ovarian cancer are awaited with interest (DUO-O [27]; ENGOT-ov43/KEYLYNK-001 [28]; FIRST/ENGOT-ov44 [29]). The phase III IMaGYN050 trial evaluating the addition of the programmed cell death ligand 1 (PD-L1) inhibitor atezolizumab to platinum-based chemotherapy with bevacizumab did not meet its co-primary endpoint of PFS, although the timing of surgery and residual disease status appeared to impact treatment outcomes [30].

5. Conclusions

Results of this post hoc exploratory analysis indicate that combination therapy with maintenance olaparib plus bevacizumab should be considered for all HRD-positive patients with newly diagnosed, advanced ovarian cancer, regardless of whether they are considered at higher or lower risk of disease progression. Future trials in newly diagnosed advanced ovarian cancer should include all patients, irrespective of their risk factors.

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Declaration of Competing Interest

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Appendix A. Supplementary data

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References

[1] J.A. Ledermann, F.A. Raja, C. Fotopoulou, A. Gonzalez-Martin, N. Colombo, C. Sessa, et al., Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 Suppl 6 (2013) vi24–32.

[2] A. du Bois, A. Reuss, E. Pujade-Lauraine, P. Harter, I. Ray-Coquard, J. Pfisterer, Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux pour les etudes des cancers de l'Ovaire (GINECO), Cancer 115 (2009) 1234–1244.

[3] R.A. Burger, M.F. Brady, M.A. Bookman, G.F. Fleming, B.J. Monk, H. Huang, et al., Incorporation of bevacizumab in the primary treatment of ovarian cancer, N. Engl. J. Med. 365 (2011) 2473–2483.

[4] T.J. Perren, A.M. Swart, J. Pfisterer, J.A. Ledermann, E. Pujade-Lauraine, G. Kristensen, et al., A phase 3 trial of bevacizumab in ovarian cancer, N. Engl. J. Med. 365 (2011) 2484–2496.

[5] K.S. Tewari, R.A. Burger, D. Enserro, B.M. Norquist, E.M. Swisher, M.F. Brady, et al., Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer, J. Clin. Oncol. 37 (2019) 2317–2328.

[6] A.M. Oza, A.D. Cook, J. Pfisterer, A. Embleton, J.A. Ledermann, E. Pujade-Lauraine, et al., Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial, Lancet Oncol. 16 (2015) 928–936.

[7] K. Moore, N. Colombo, G. Scambia, B.G. Kim, A. Oaknin, M. Friedlander, et al., Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer, N. Engl. J. Med. 379 (2018) 2495–2505.

[8] AstraZeneca, LYNPARZA® (olaparib) Tablets, for Oral Use: Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s013lbl.pdf 2021 (accessed 24 March 2021).

[9] AstraZeneca, Lynparza Summary of Product Characteristics, https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf 2021 (accessed 24 March 2021).

[10] AstraZeneca, Lynparza Approved in China as a 1st-line Maintenance Therapy in BRCA-mutated Advanced Ovarian Cancer, https://www.astrazeneca.com/media-centre/press-releases/2019/lynparza-approved-in-china-as-a-1st-line-maintenance-therapy-in-brca-mutated-advanced-ovarian-cancer.html 2019 (accessed 27 April 2020).

[11] AstraZeneca, Lynparza Approved in Japan for 1st-line Maintenance Therapy in BRCA-mutated Advanced Ovarian Cancer, https://www.astrazeneca.com/media-centre/press-releases/2019/lynparza-approved-in-japan-for-1st-line-maintenance-therapy-in-brca-mutated-advanced-ovarian-cancer-19062019.html 2019 (accessed 26 May 2020).

[12] I. Ray-Coquard, P. Pautier, S. Pignata, D. Perol, A. Gonzalez-Martin, R. Berger, et al., Olaparib plus bevacizumab as first-line maintenance in ovarian cancer, N. Engl. J. Med. 381 (2019) 2416–2428.

[13] AstraZeneca, Lynparza Approved in Japan for the Treatment of Advanced Ovarian, Prostate and Pancreatic Cancers, https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/lynparza-approved-in-japan-for-three-cancers.html 2020 (accessed 15 February 2021).

[14] A. Gonzalez-Martin, B. Pothuri, I. Vergote, R. DePont Christensen, W. Graybill, M.R. Mirza, et al., Niraparib in patients with newly diagnosed advanced ovarian cancer, N. Engl. J. Med. 381 (2019) 2391–2402.

[15] I. Vergote, E. Pujade-Lauraine, S. Pignata, G.B. Kristensen, J. Ledermann, A. Casado, et al., European network of Gynaecological oncological trial Groups' requirements for trials between academic groups and pharmaceutical companies, Int. J. Gynecol. Cancer 20 (2010) 476–478.

[16] A. du Bois, A. Reuss, E. Pujade-Lauraine, S. Pignata, J. Ledermann, A. Casado, 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 (2015) 1328–1330.

[17] P. Harter, Z.M. Muallem, C. Buhrmann, D. Lorenz, C. Kaub, R. Hils, et al., Impact of a structured quality management program on surgical outcome in primary advanced ovarian cancer, Gynecol. Oncol. 121 (2011) 615–619.

[18] J.H. Tseng, R.A. Cowan, Q. Zhou, A. Iasonos, M. Byrne, T. Polcino, et al., Continuous improvement in primary Debulking surgery for advanced ovarian cancer: do increased complete gross resection rates independently lead to increased progression-free and overall survival? Gynecol. Oncol. 151 (2018) 24–31.

[19] C. Fotopoulou, N. Concin, F. Planchamp, P. Morice, I. Vergote, A. du Bois, et al., Quality indicators for advanced ovarian cancer surgery from the European Society of Gynaecological Oncology (ESGO): 2020 update, Int. J. Gynecol. Cancer 30 (2020) 436–440.

[20] M. Hall, K. Savvatis, K. Nixon, M. Kyrgiou, K. Hariharan, M. Padwick, et al., Maximal-effort cytoreductive surgery for ovarian cancer patients with a high tumor burden: variations in practice and impact on outcome, Ann. Surg. Oncol. 26 (2019) 2943–2951.

[21] A.L. Covens, A critique of surgical cytoreduction in advanced ovarian cancer, Gynecol. Oncol. 78 (2000) 269–274.

[22] A. du Bois, G. Kristensen, I. Ray-Coquard, A. Reuss, S. Pignata, N. Colombo, et al., Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial, Lancet Oncol. 17 (2016) 78–89.

[23] R.L. Coleman, G.F. Fleming, M.F. Brady, E.M. Swisher, K.D. Steffensen, M. Friedlander, et al., Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer, N. Engl. J. Med. 381 (2019) 2403–2415.

[24] A. Gonzalez Martin, A.M. Oza, A.C. Embleton, J. Pfisterer, J.A. Ledermann, E. Pujade-Lauraine, et al., Exploratory outcome analyses according to stage and/or residual disease in the ICON7 trial of carboplatin and paclitaxel with or without bevacizumab for newly diagnosed ovarian cancer, Gynecol. Oncol. 152 (2019) 53–60.

[25] ENGOT, Ovarian Cancer Clinical Trials: ENGOT-ov63/GINECO/NIRVANA, https://engot.esgo.org/clinical-trials/current-clinical-trials/ovarian/ 2021 (accessed 22 September).

[26] B.M. Norquist, M.F. Brady, M.I. Harrell, T. Walsh, M.K. Lee, S. Gulsuner, et al., Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: an NRG oncology/gynecologic oncology group study, Clin. Cancer Res. 24 (2018) 777–783.

[27] P. Harter, M. Bidzinski, N. Colombo, A. Floquet, M.J. Rubio-Perez, J.W. Kim, et al., DUO-O: a randomized phase III trial of durvalumab (durva) in combination with chemotherapy and bevacizumab (bev), followed by maintenance durva, bev and olaparib (olap), in newly diagnosed advanced ovarian cancer patients [abstract], J. Clin. Oncol. 37 (2019) TPS5598.

[28] I. Vergote, J. Sehouli, V. Salutari, P. Zola, R. Madry, R.M. Wenham, et al., ENGOT-OV43/KEYLYNK-001: a phase III, randomized, double-blind, active- and placebo-controlled study of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of BRCA-nonmutated advanced epithelial ovarian cancer [abstract], J. Clin. Oncol. 37 (2019) TPS5603.

[29] A.C. Hardy-Bessard, K.N. Moore, M.R. Mirza, B. Asselain, A. Redondo, J. Pfisterer, et al., ENGOT-OV44/FIRST study: a randomized, double-blind, adaptive, phase III study of platinum-based therapy with dostarlimab (TSR-042) + niraparib versus standard-of-care (SOC) platinum-based therapy as first-line treatment of stage 3/4 non-mucinous epithelial ovarian cancer (OC) [abstract], J. Clin. Oncol. 37 (2019) TPS5600.

[30] K.N. Moore, M. Bookman, J. Sehouli, A. Miller, C. Anderson, G. Scambia, et al., Primary results from IMagyn050/GOG 3015/ENGOT-OV39, a double-blind placebo (pbo)-controlled randomised phase III trial of bevacizumab (bev)-containing therapy +/− atezolimumab (atezo) for newly diagnosed stage III/IV ovarian cancer (OC) [abstract], Ann. Oncol. 31 (Suppl. 4) (2020) LBA31.