MaNGO
Mario Negri Gynecologic Oncology

Antiangiogenetici e Parp inibitori in prima linea: quale algoritmo nel 2021?

A. Gadducci, Pisa

XVIII ASSEMBLEA MANGO

Ricerca Clinica e Traslazionale in Ginecologia Oncologica

MILANO, 2-3 LUGLIO 2021

Con il Patrocinio di:

AIOM Associazione Italiana di Oncologia Medica

FICOG | Federation of Italian Cooperative Oncology Groups

SOCIETA' ITALIANA DI CANCEROLOGIA

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ACTO ALLEANZA CONTRO IL TUMORE OVARICO

Consolidation and maintenance therapy for advanced EOC pts in complete response after first-line CT

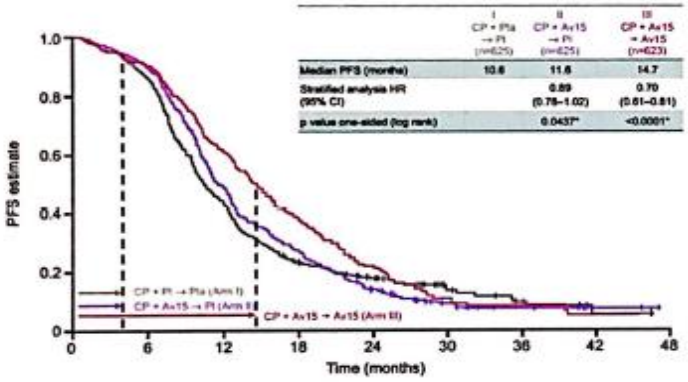
- ✓ Whole abdomen radiotherapy
- ✓ Intraperitoneal chromic phosphate (32P)
- ✓ Radioimmunotherapy
- ✓ Intraperitoneal chemotherapy
- ✓ High-dose chemotherapy with hematopoietic support
- ✓ Prolonged administration of 1-line chemotherapy
- ✓ Concomitant or sequential addition of a third cytotoxic agent to CBDCA/PTX

ANTI-VEGF TARGETING: BEVACIZUMAB in FRONT-LINE

NSGO-CTU · Rigshospitalet · ENGOT

PFS

Bevacizumab GOG-218

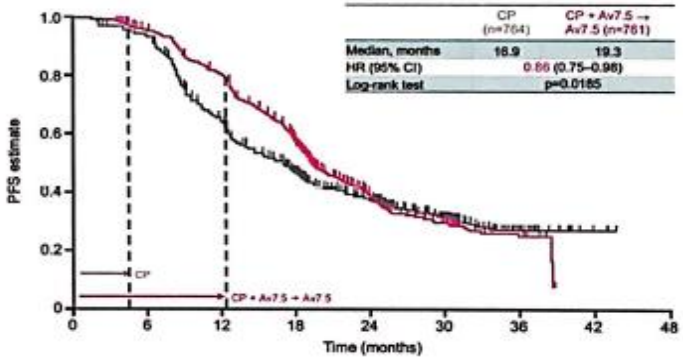


	I CP + Pla → Pl (n=625)	II CP + Av15 → Pl (n=625)	III CP + Av15 → Av15 (n=623)
Median PFS (months)	10.6	11.8	14.7
Stratified analysis HR (95% CI)		0.89 (0.78–1.02)	0.70 (0.61–0.81)
p value one-sided (log rank)		0.0437*	<0.0001*

HR: 0.73
10.4 vs 13.9 mos
Median D: 3.5 mos

Burger et al. *N Engl J Med 2011*

Bevacizumab ICON7



	CP (n=764)	CP + Av7.5 → Av7.5 (n=761)
Median, months	18.9	19.3
HR (95% CI)	0.86 (0.75–0.98)	
Log-rank test	p=0.0185	

HR: 0.87
17.4vs 19.8 mos
Median D: 2.4 mos

Perren T... Mirza MR et al. *N Engl J Med 2011*

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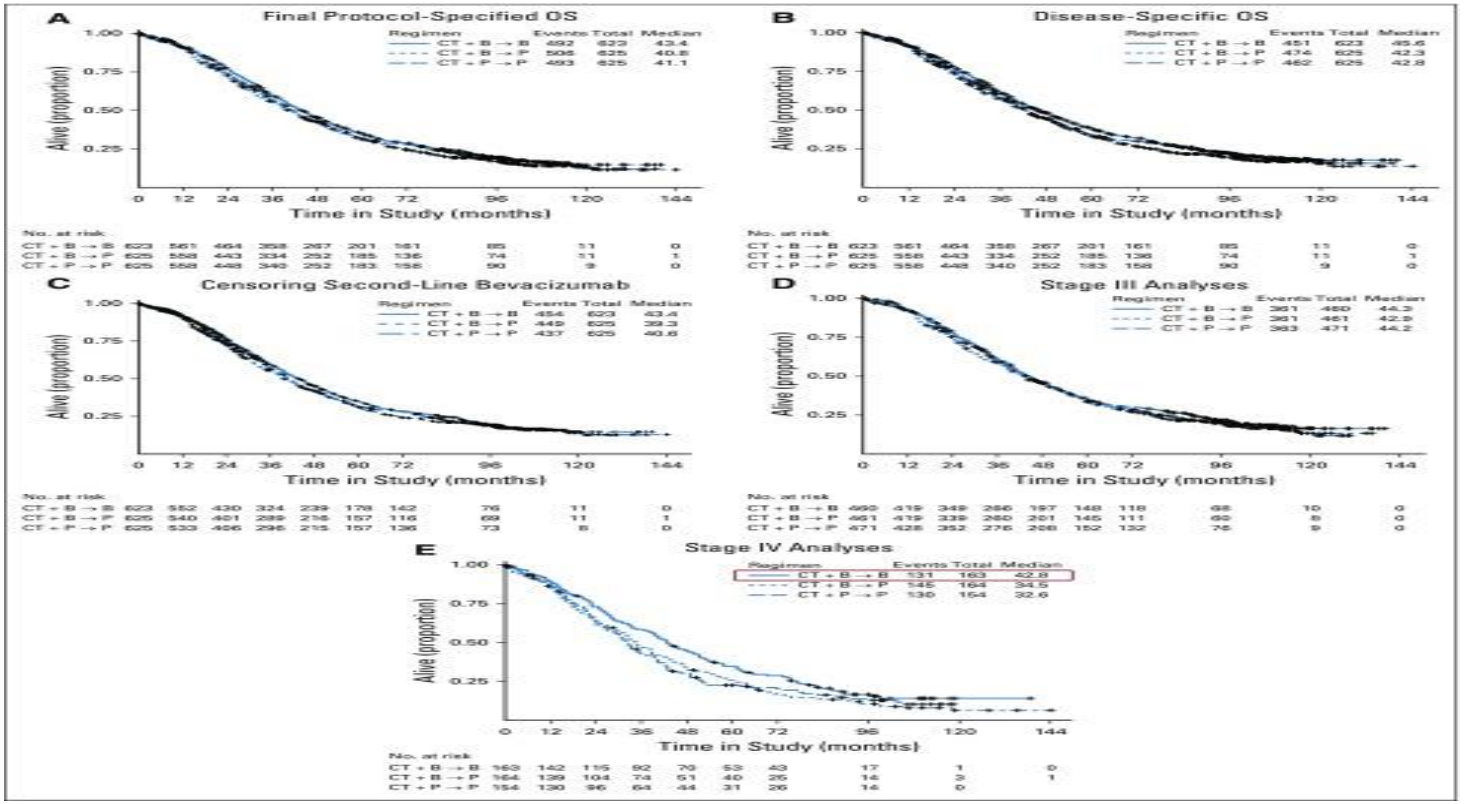
GOG 218 TRIAL



Standard CT ± BEV for pts with newly diagnosed EOC (ICON7): OS results of a phase 3 randomised trial

	All pts		High-risk pts*	
	CT	CT + BEV	CT	CT+ BEV
OS (95% CI) (months)	58,6 53,5-67,5	58,0 52,4-66,9	30,2 27,0-34,3	39,7 36,0-44,2
P value		0,85		0,03

*stage IV, inoperable stage III, or suboptimally debulked (>1 cm) stage III

Oza et al, Lancet Oncol. 2015

Exploratory outcome analyses according to stage and/or RD in the ICON7 trial for newly diagnosed EOC

PFS (months)

	Stage III-b-IV (no RD) (n. 411)	Stage III-b-IV (RD) (n.749)
CT + BEV	29,5	16,7
CT	24,3	12,0
HR (95%CI)	0.77 (0.59.0.99)	0.81 (0.69–0.95)

Gonzalez Martinet et al. 2019

Incorporation of BEV in first- line therapy of EOC : Real World observational studies

NCT01697488:	Non-interventional Surveillance Study on First-line BEV in Combination With CBDCA/PTX in Patients With Advanced Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer (OTILIA)
NCT01863693:	Observational Study of BEV in Combination With Chemotherapy as First-Line Treatment in Patients With Advanced Ovarian Cancer (OSCAR1)
JGOG3022:	BEV Combined with platinum–taxane chemotherapy as first-line treatment for advanced ovarian cancer: a prospective observational study of safety and efficacy in Japanese patients (Komiyama et al.)
ROBOT TRIAL:	Real-World Study of Adding BEV to Chemotherapy for Ovarian, Tubal, and Peritoneal Cancer as Front-Line or Relapse Therapy

BEV combined with platinum-taxane CT as 1st-line treatment for advanced EOC: a prospective observational study of safety and efficacy in Japanese patients (JGOG3022 trial)

346 (293 evaluable) pts prospectively enrolled stage III -IV EOC to receive PTX + CBDCA q3w Cycles 1-6 + BEV q3w Cycles 2-22-> median PFS= 16.3 months

	n	Response rate (in pts with measurable RD)	
		%	95% CI
All cases	89	77.5	67.4–85.7
Serous	60	81.7	69.6–90.5
Endom	10	80	44.4–97.5
Clear cell	11	63.6	30.8–89.1
Others	8	62.5	24.5–91.5

Response rate to PTX/CBDCA: 46.7% in ovarian CCC (Sugiyama 2016)

Incorporation of BEV in first- line therapy of EOC : Real World observational studies

NCT01239732 ROSIA	Global Study to Assess the Addition of BEV to CBDCA + PTX as Front-line Treatment of Epithelial Ovarian Cancer, Fallopian Tube Carcinoma or Primary Peritoneal carcinoma
NCT01706120: MITO16/MANGO-2	Study of Clinical and Biological Prognostic Factors in Patients With Ovarian Cancer Receiving CBDCA +PTX With BEV
NCT01462890: BOOST	A Prospective Randomised Phase III Trial to Evaluate Optimal Treatment Duration of First-line BEV in Combination With CBDCA + PTX in Patients With Primary Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer

Efficacy and safety of BEV -containing therapy in newly diagnosed EOC : ROSiA Single-Arm Phase 3B Study

- ✓ 1021 pts with G3 stage I-IIA or IIB-IV EOC (Eligibility criteria similar to ICON 7)
- ✓ BEV [15 mg/kg (89%) or 7.5 mg/kg q3w] + PTX [175 mg/m^2 q3w or 80 mg/m^2 weekly] + CBDCA [AUC5-6 q3w for 4-8 cycles], followed by BEV maintenance for up to 24 months
- ✓ BEV for > 1 year: 62%, > 15 months: 53%, and > 2 years: 29%
- ✓ Median PFS: 25.5 months (in the whole series)

  18.3 months in high-risk patients

  32.0 months in non high-risk patients

Oza et al 2017

Efficacy and safety of BEV -containing therapy in newly diagnosed EOC : ROSiA Single-Arm Phase 3B Study

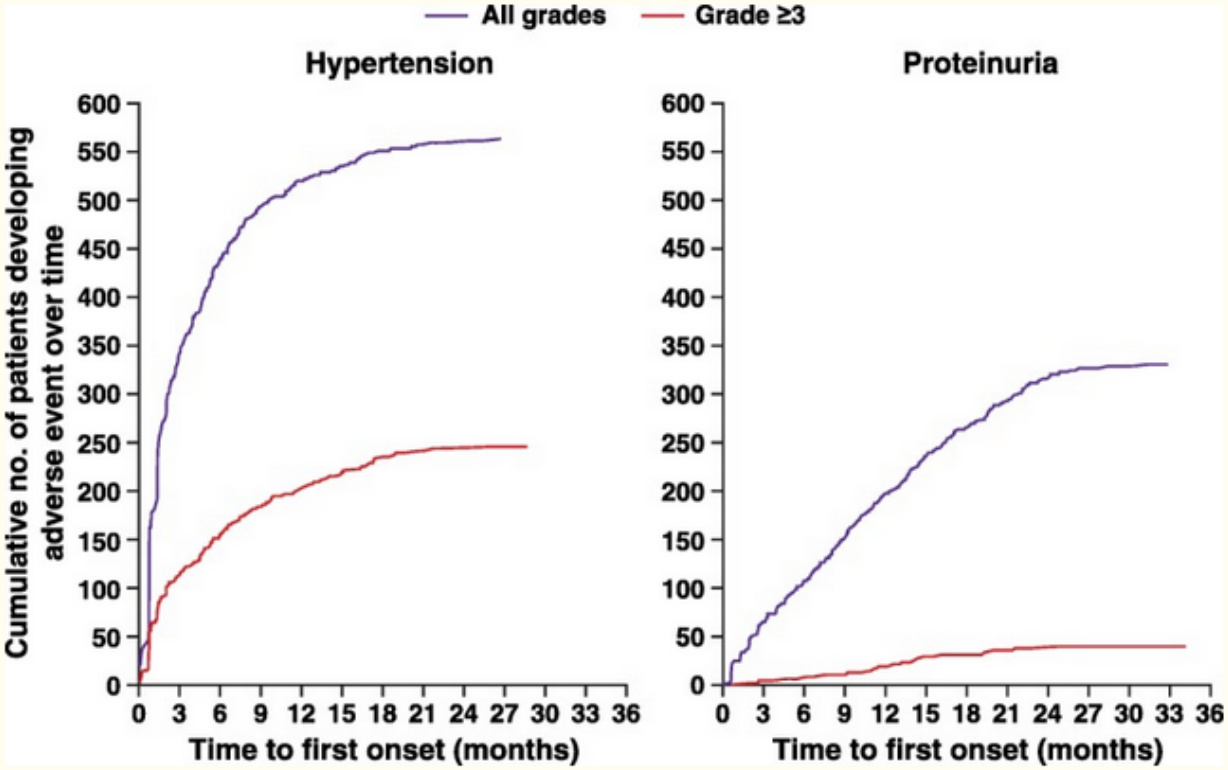


FIGURE 2

Cumulative number of patients developing hypertension or proteinuria over time.

BEV + CBDCA+ PTX in the 1st line treatment of advanced EOC patients: the phase IV MITO-16A/MaNGO-OV2A study

- ✓ 398 pts :CBDCA (AUC 5) PTX (175 mg/m^2) + BEV (15 mg/kg) q3w x 6 cycles followed by BEV until cycle 22nd (Median follow-up: 32.3 months)
- ✓ Median PFS: 20.8 months, median OS: 41.1 months. Efficacy and toxicity profile comparable to previous data.
- ✓ Prognostic variables PS, stage, and RD after primary surgery.
- ✓ Neither baseline PA nor the development of hypertension during BEV were prognostic factors.

Daniele et al 2021

Optimal treatment duration of BEV combined with CBDCA/PTX in pts with primary EOC: a multicenter open-label randomized 2-arm phase 3 ENGOT/GCIG trial of the AGO Study Group, GINECO, and NSGO (BOOST)

- ✓ 927 stage IIB–IV EOC pts treated with PDS and PTX (175 mg/m^2) + CBDCA AUC 5 + BEV 15 mg/kg q3w

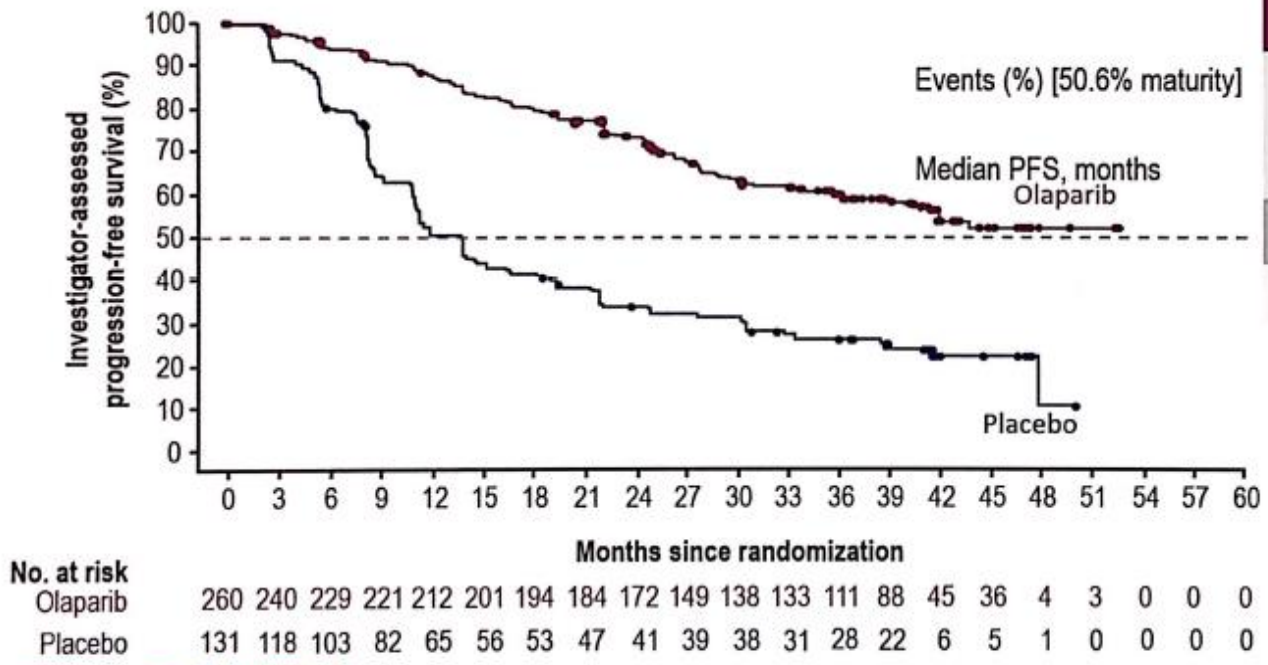
RANDOM

	BEV x 15 months	BEV x 30 months	HR (95% CI)
median PFS (months)	24.2	26.0	0.99 (0.85-1.15)
median OS (months)	54.3	60.0	1.04 (0.87–1.23)

Efficacy according to BRCA and genomic instability

	PRIMA	SOLO1	VELIA	PAOLA 1
ITT	HR 0.62 0.5-0,76	HR 0,30 0.23-0,41	HR 0,68 0,56-0,83	HR 0.59 0,49-0,72
HRD	HR 0.43 0.31-0,59		HR 0.57 0.43-0,76	HR 0.33 0.25-0,45
HRD+BRCAm	HR 0.40 0,27-0,62	HR 0,30 0.23-0,41	HR 0.44 0.28-0,68	HR 0.31 0.2-0,47
HRD+BRCAwt	HR 0,50 0.31-0,83			HR 0.43 0.28-0,66
HRP	HR 0.68 0.49-0,94		HR 0.81 0.6-1,09	HR 0.92 0.72-1,17

SOLO1: OLAPARIB in BRCAmut POPULATION: PFS



	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		

CI, confidence interval; NR, not reached

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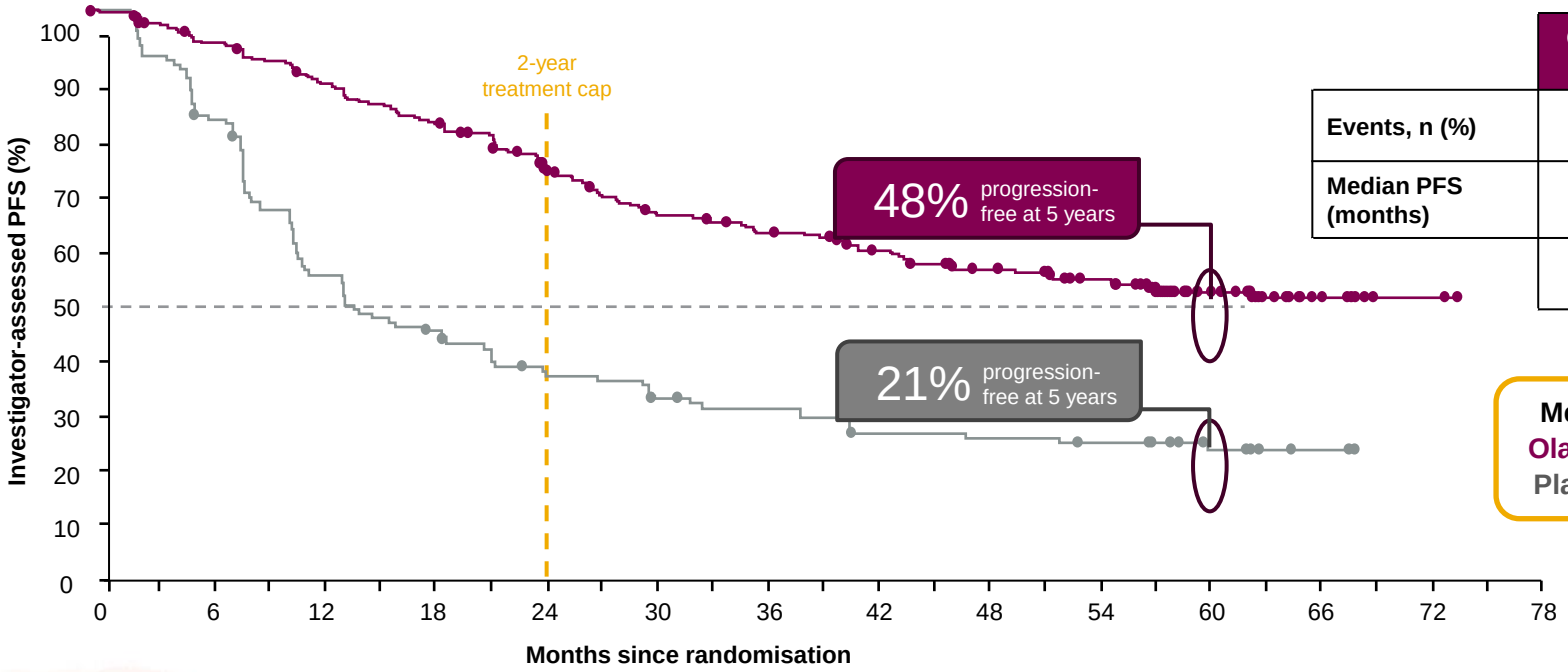
Moore K et al. ***New Engl J Med 2018***

SOLO1: After 5 years follow up the PFS benefit derived maintenance olaparib was sustained substantially beyond the end of treatment



	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)
Median PFS (months)	56.0	13.8
	HR 0.33 95% CI 0.25–0.43	

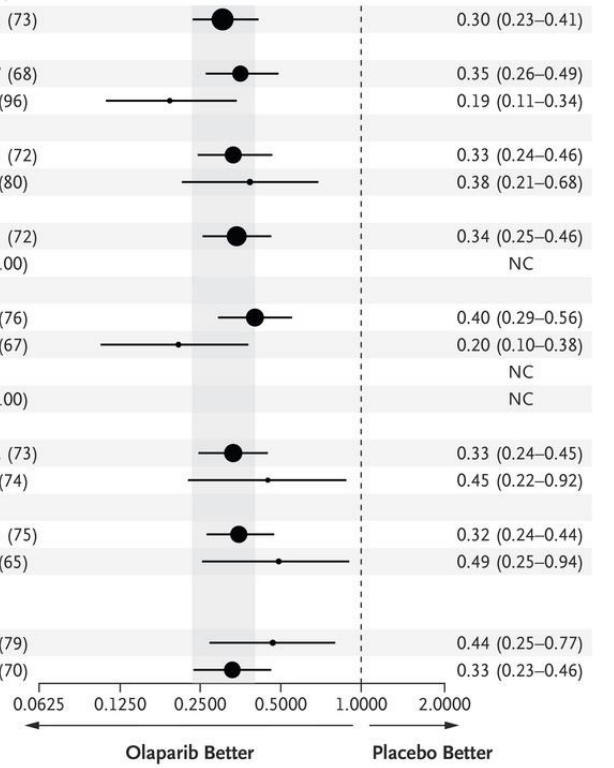
Median follow up
Olaparib: 4.8 years
Placebo: 5.0 years

Investigator-assessed PFS
DCO: March 2020; Median follow-up: olaparib, 4.8 years, placebo, 5.0 years
CI=confidence interval; HR=hazard ratio; PFS=progression-free survival

Banerjee S, et al. Presented at ESMO Virtual Congress 2020, 19-21 September, Abstract #811MO

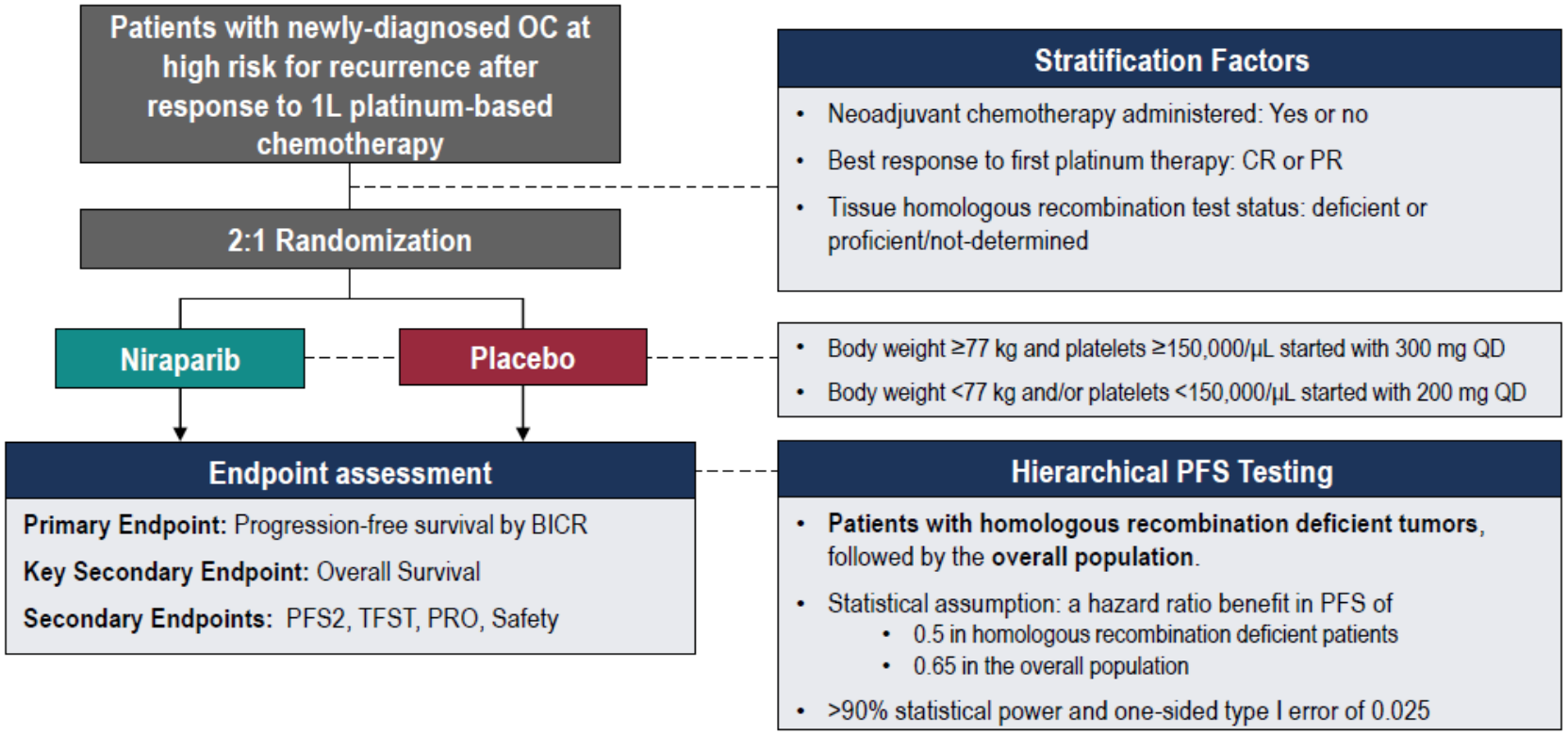
Maintenance olaparib in pts with newly diagnosed advanced EOC

Subgroup	Olaparib	Placebo
	no. of patients with disease progression or death/total no. (%)	
All patients	102/260 (39)	96/131 (73)
Clinical response after chemotherapy		
Complete response	73/213 (34)	73/107 (68)
Partial response	29/47 (62)	23/24 (96)
ECOG performance status at baseline		
Normal activity	75/200 (38)	76/105 (72)
Restricted activity	27/60 (45)	20/25 (80)
CA-125 level at baseline		
≤ULN	92/247 (37)	89/123 (72)
>ULN	10/13 (77)	7/7 (100)
Germline *BRCA* mutation according to testing at Myriad		
BRCA1	84/188 (45)	69/91 (76)
BRCA2	15/62 (24)	26/39 (67)
BRCA1 and *BRCA2*	0/3	0/0
None	3/7 (43)	1/1 (100)
Age at baseline		
<65 yr	85/225 (38)	82/112 (73)
≥65 yr	17/35 (49)	14/19 (74)
International FIGO stage at initial diagnosis		
Stage III	83/220 (38)	79/105 (75)
Stage IV	19/40 (48)	17/26 (65)
Presence of residual macroscopic disease after debulking surgery performed before trial entry		
Yes	29/55 (53)	23/29 (79)
No	70/200 (35)	69/98 (70)



Banerjee et al. 2021

PRIMA Trial Design



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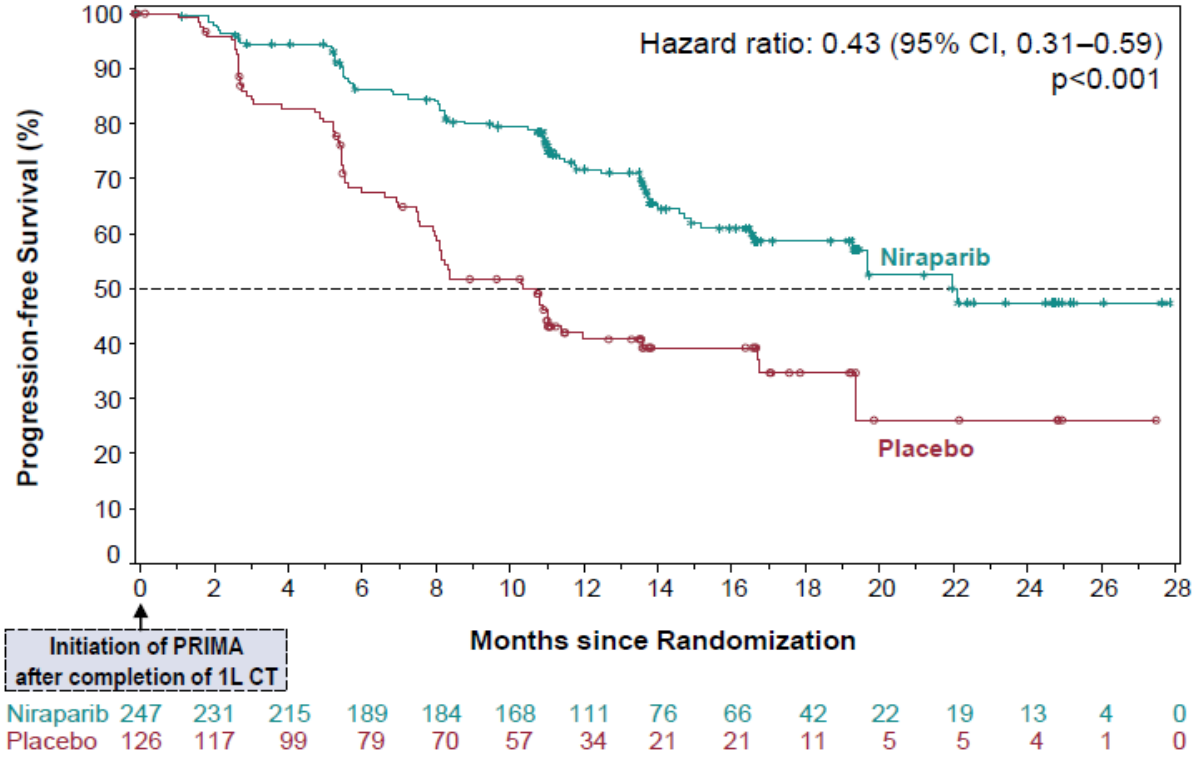
1L, first-line; BICR, blinded independent central review; CR, complete response; OC, ovarian cancer; PFS2, progression-free survival 2; PR partial response; PRO, patient-reported outcomes; TFST, time to first subsequent therapy.

PRIMA Primary Endpoint, PFS Benefit in the HR-deficient Population



57% reduction in risk of relapse or death with niraparib

	Niraparib (n=247)	Placebo (n=126)
Median PFS		
months (95% CI)	21.9 (19.3–NE)	10.4 (8.1–12.1)
Patients without PD or death (%)		
6 months	86%	68%
12 months	72%	42%
18 months	59%	35%

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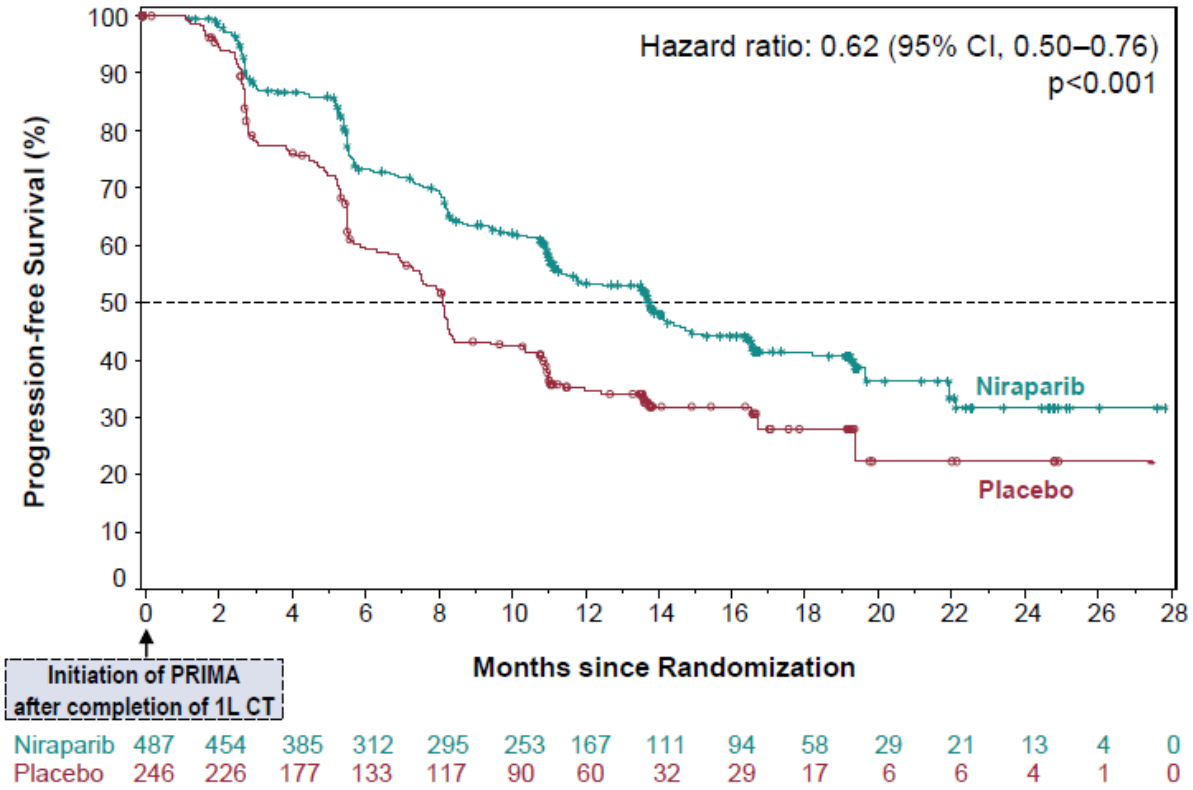
1L, first-line; CI, confidence interval; CT, chemotherapy; HR, homologous recombination; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

PRIMA Primary Endpoint, PFS Benefit in the Overall Population



38% reduction in risk of relapse or death with niraparib

	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

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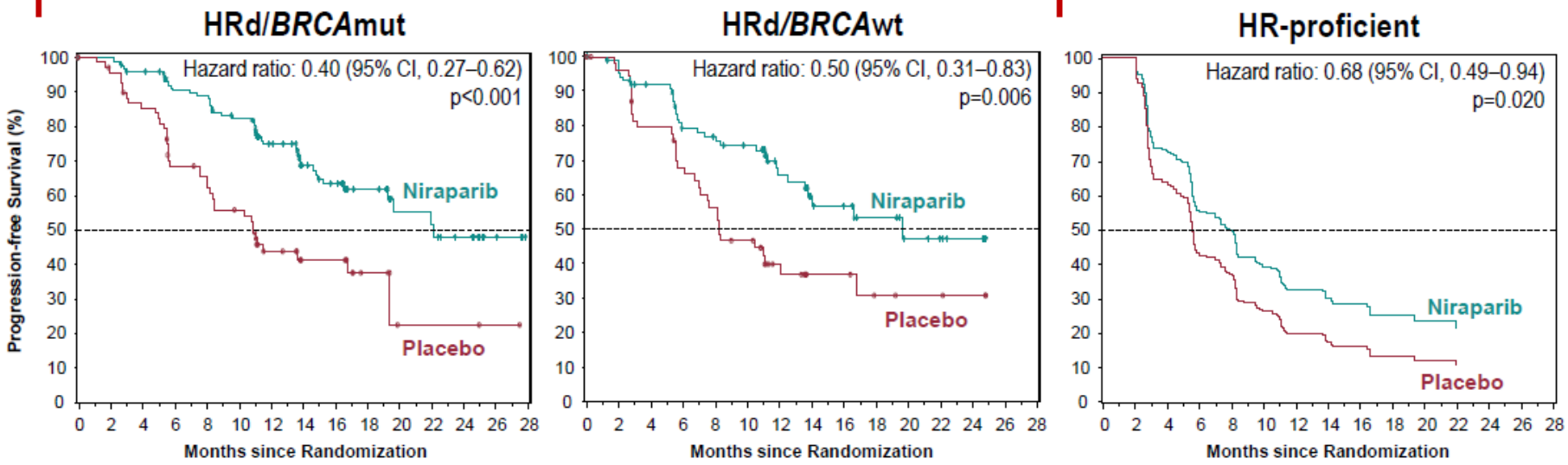
1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.

PRIMA PFS Benefit in Biomarker Subgroups

Homologous Recombination Deficient (HRd)



- Niraparib provided similar clinical benefit in the HRd subgroups (*BRCA*mut and *BRCA*wt)
- Niraparib provide clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

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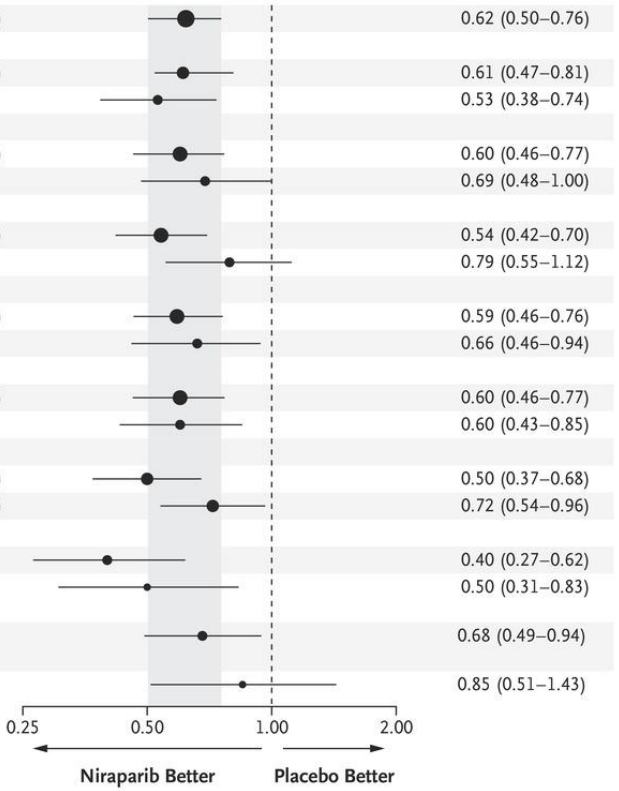
CI, confidence interval; HR, homologous recombination; mut, mutation; PFS, progression-free survival wt, wild-type.

Niraparib in pts with newly diagnosed advanced EOC

Subgroup	Niraparib	Placebo
	no. of patients with disease progression or death/total no. (%)	
All patients	232/487 (47.6)	155/246 (63.0)
Age		
<65 yr	136/297 (45.8)	86/147 (58.5)
≥65 yr	96/190 (50.5)	69/99 (69.7)
ECOG score		
0	146/337 (43.3)	107/174 (61.5)
1	86/150 (57.3)	48/72 (66.7)
Stage of disease at initial diagnosis		
III	143/318 (45.0)	103/158 (65.2)
IV	89/169 (52.7)	52/88 (59.1)
Neoadjuvant chemotherapy		
Yes	151/322 (46.9)	107/167 (64.1)
No	81/165 (49.1)	48/79 (60.8)
Best response to platinum therapy		
Complete response	146/337 (43.3)	100/172 (58.1)
Partial response	86/150 (57.3)	55/74 (74.3)
Geographic region		
North America	104/218 (47.7)	82/115 (71.3)
All other regions	128/269 (47.6)	73/131 (55.7)
Homologous-recombination status		
BRCA mutation	49/152 (32.2)	40/71 (56.3)
No *BRCA* mutation, homologous-recombination deficiency	32/95 (33.7)	33/55 (60.0)
Homologous-recombination proficiency	111/169 (65.7)	56/80 (70.0)
Not determined	40/71 (56.3)	26/40 (65.0)



Gonzales-martin et al. 2019

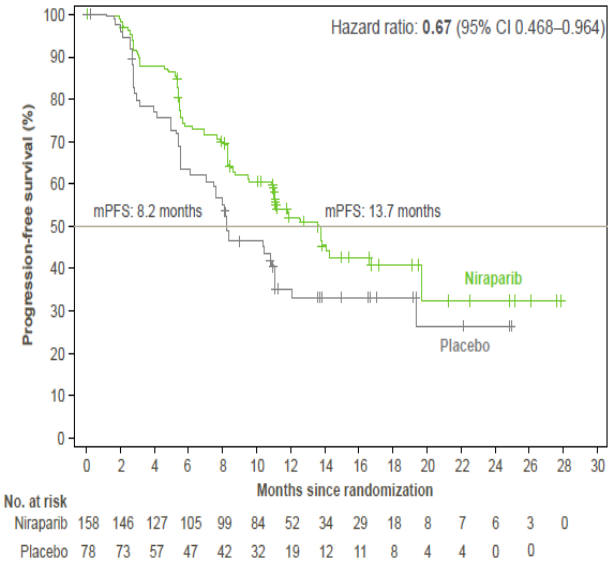
Niraparib in pts with newly diagnosed advanced EOC

Different populations of SOLO1 and PRIMA trials (not only as for BRCA or HRD)

More pts in SOLO 1 had stage III disease (83% versus 65%) and underwent PDS with no macroscopic RD (44% versus 0.4%)

	Risk of progression HR (95% CI)
Olaparib-treated pts with RD after surgery (SOLO1 trial)	0.44 (0.25-0.77)
Niraparib- treated pts with BRCA mutation and RD after surgery (PRIMA trial)	0.40 (0.27- 0.62)

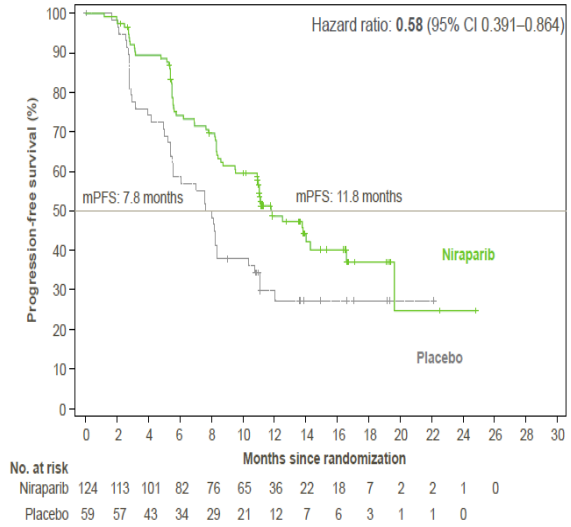
PFS by surgical status – Primary debulking surgery



In patients who received PDS, 16 patients' residual disease status was unknown.
CI, confidence interval; HR, hazard ratio; mPFS, median PFS; PDS, primary debulking surgery; PFS, progression-free survival.
O'Cearbhaill R, et al. presented at SGO 2021, 19–25 Mar (virtual).

PDS

PFS by surgical and VRD status – Primary debulking surgery with visible residual disease



CI, confidence interval; HR, hazard ratio; mPFS, median PFS; PDS, primary debulking surgery; PFS, progression-free survival; VRD, visible residual disease.
O'Cearbhaill R, et al. presented at SGO 2021, 19–25 Mar (virtual).

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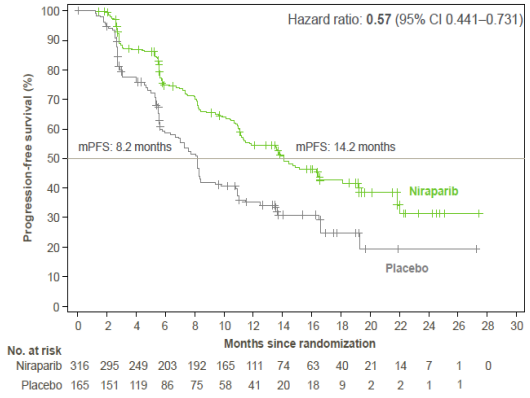
IDS

PFS by surgical status – Interval debulking surgery



No. at risk														
Niraparib	316	295	249	203	192	165	111	74	63	40	21	14	7	1	0
Placebo	165	151	119	86	75	58	41	20	18	9	2	2	1	1	

In patients who received IDS, 28 patients' residual disease status was unknown.
CI, confidence interval; HR, hazard ratio; IDS, interval debulking surgery; mPFS, median PFS; PFS, progression-free survival.
O'Cearbhaill R, et al. presented at SGO 2021, 19–25 Mar (virtual).

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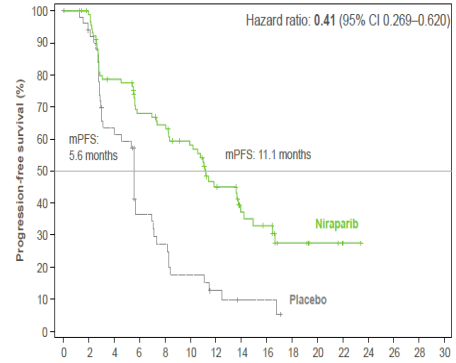
PFS by surgical and VRD status – Interval debulking surgery with visible residual disease



No. at risk														
Niraparib	96	88	68	56	52	44	26	17	14	7	4	1	0	
Placebo	53	46	30	15	11	7	4	2	2	0				

CI, confidence interval; HR, hazard ratio; IDS, interval debulking surgery; mPFS, median PFS; PFS, progression-free survival; VRD, visible residual disease.
O'Cearbhaill R, et al. presented at SGO 2021, 19–25 Mar (virtual).

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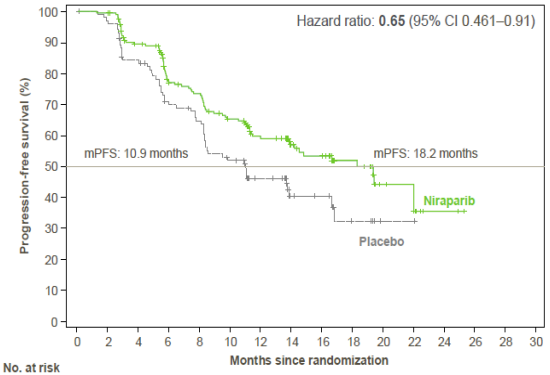
PFS by surgical and VRD status – Interval debulking surgery with no visible residual disease



No. at risk													
Niraparib	202	189	163	131	124	107	76	49	42	27	11	7	2	0
Placebo	102	97	82	66	60	47	33	14	12	6	1	1	0	

CI, confidence interval; HR, hazard ratio; IDS, interval debulking surgery; mPFS, median PFS; NVRD, no visible residual disease; PFS, progression-free survival.
O'Cearbhaill R, et al. presented at SGO 2021, 19–25 Mar (virtual).

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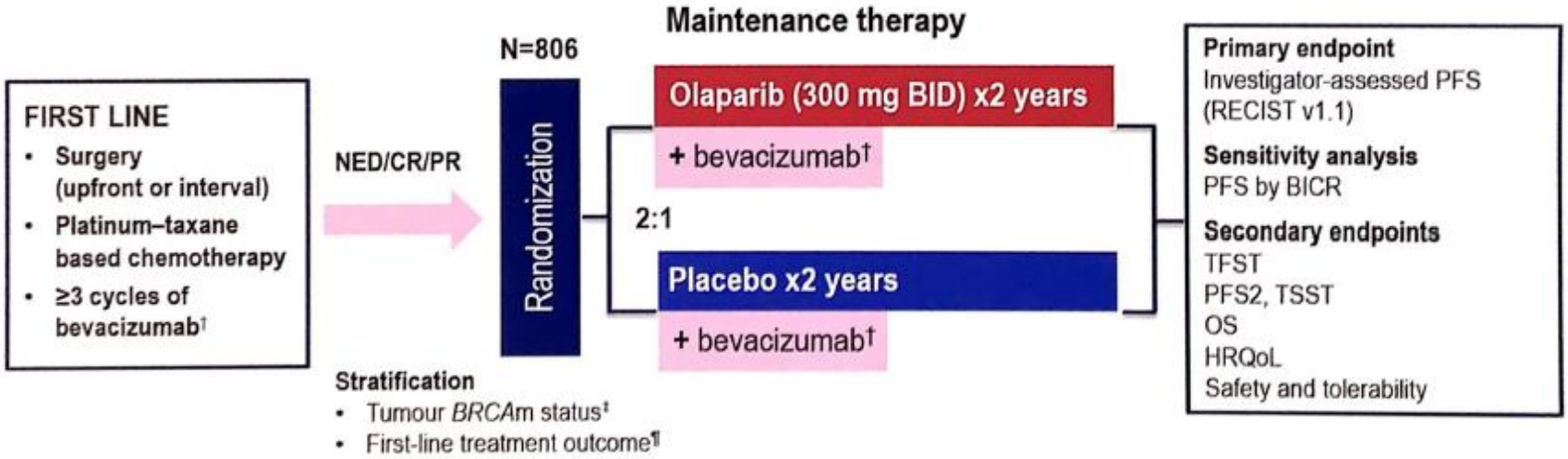
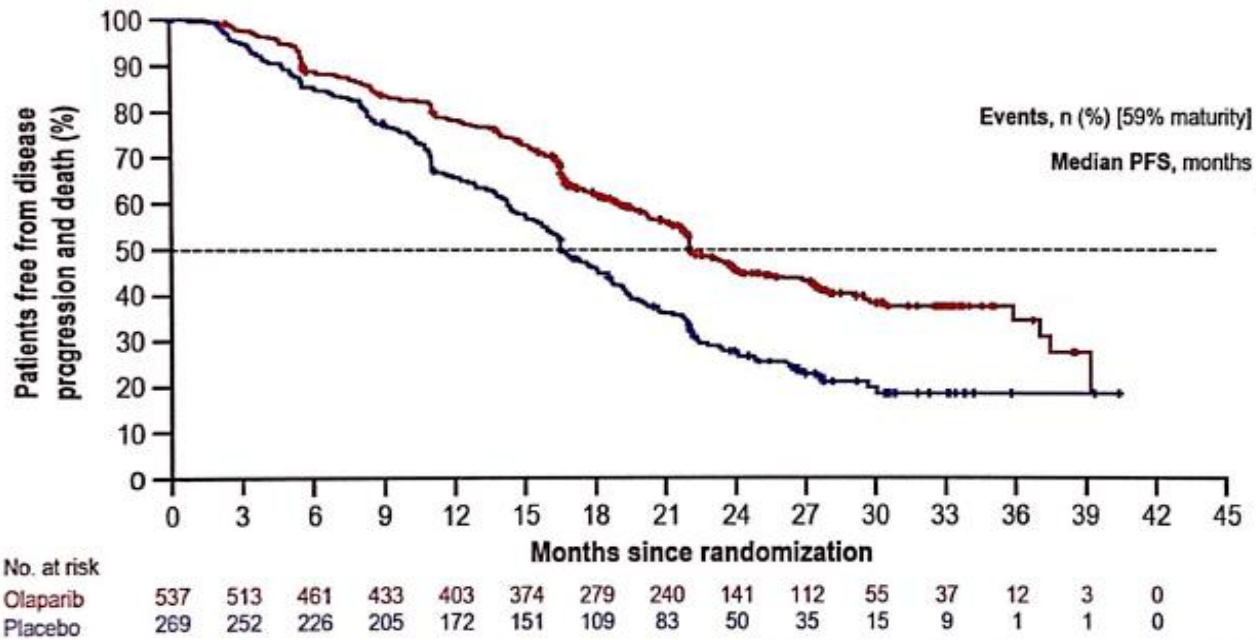
Study design

Newly diagnosed FIGO stage III–IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer*



*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

PFS by investigator assessment: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	22.1	16.6

HR 0.59 (95% CI 0.49–0.72; *P*<0.0001)

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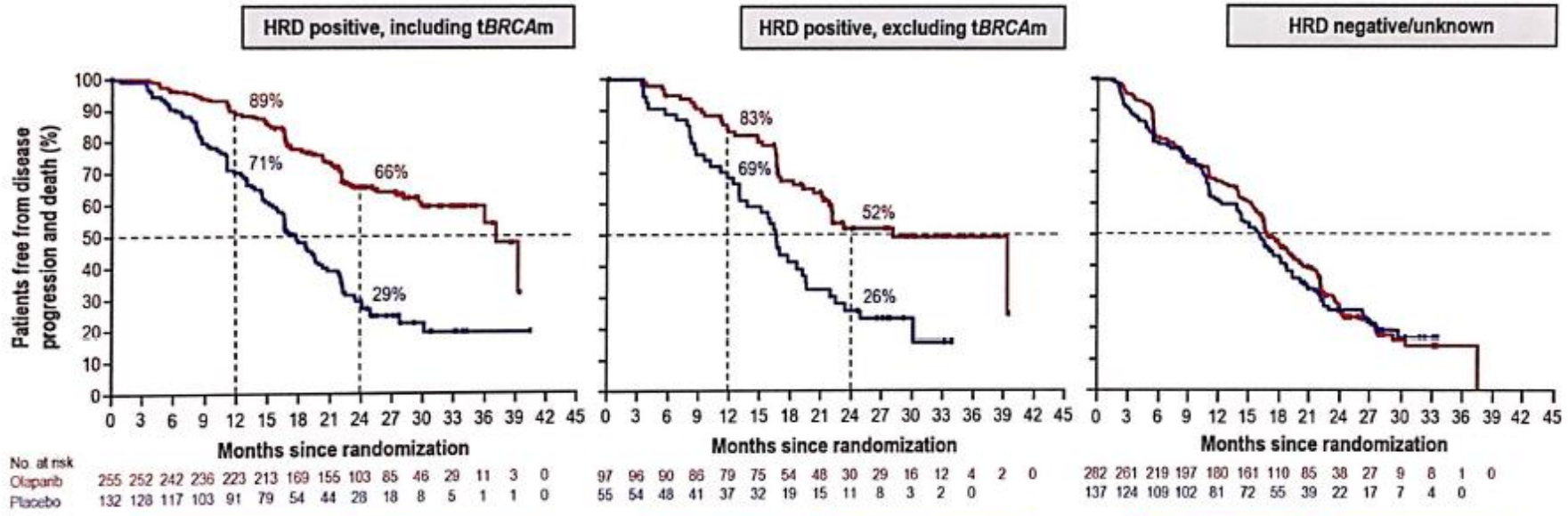
ITT, intent-to-treat population

Median time from first cycle of chemotherapy to randomization = 7 months

PFS by HRD status



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	37.2*	17.7
HR 0.33 (95% CI 0.25–0.45)		

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	28.1*	16.6
HR 0.43 (95% CI 0.28–0.66)		

	Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
Events, n (%)	193 (68)	102 (74)
Median PFS, months	16.9	16.0
HR 0.92 (95% CI 0.72–1.17)		

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42. *This median is unstable due to a lack of events – less than 50% maturity

Maintenance olaparib + BEV in pts with newly diagnosed advanced HGSOC: Final analysis of second progression-free survival (PFS2) in PAOLA-1/ENGOT-ov25 trial

	Olaparib + BEV *vs* PL + BEV	
	median PFS2 (months)	HR (95% CI)
ITT	36.5 vs 32.6	0.78 (0.64 -0.95)
BRCA mutations	NR vs 45	0.53
HRD	50.3 vs 35	0.56
HRD tumors without BRCA mutations	50.3 vs 30.1	0.60

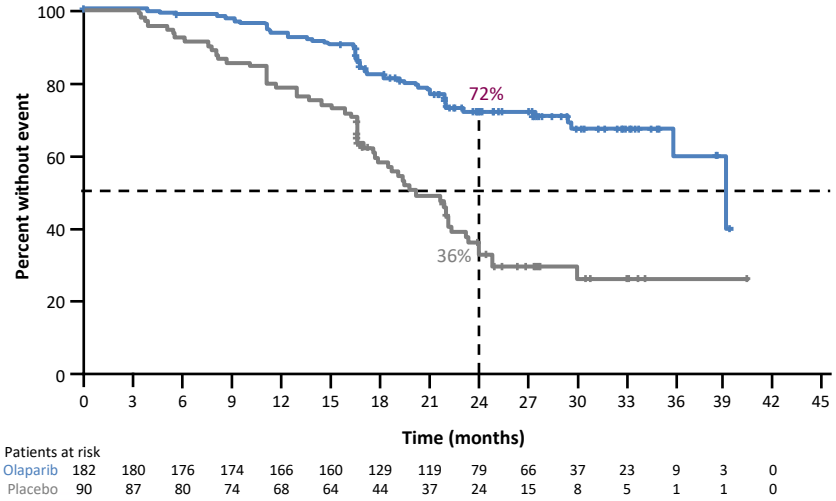
Gonzales-Martin et al. 2021

Olaparib + BEV improved PFS regardless of FIGO stage in HRD-positive pts

Stage III

Median follow-up 24.8 months

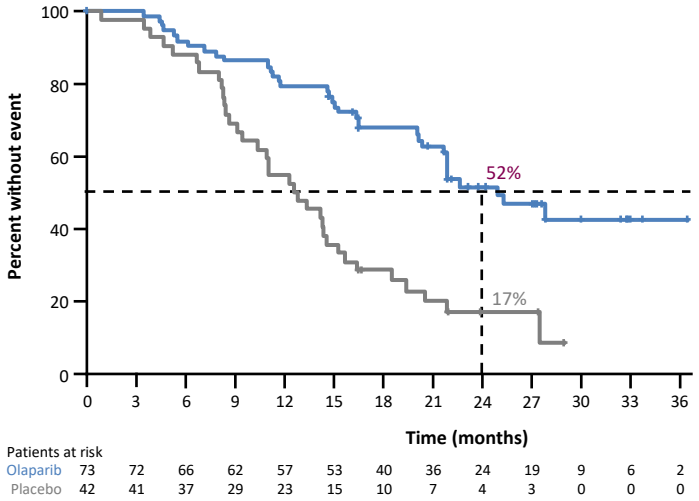
	Olaparib + bevacizumab n=182	Placebo + bevacizumab n=90
Events, n (%)	51 (28)	57 (63)
Median PFS, months	**39.3**	**19.9**
	HR 0.32 95% CI 0.22–0.47	



Stage IV

Median follow-up 24.0 months

	Olaparib + bevacizumab n=73	Placebo + bevacizumab n=42
Events, n (%)	36 (49)	35 (83)
Median PFS, months	**25.1**	**12.8**
	HR 0.32 95% CI 0.20–0.52	



DCO 22 March 2019.

*HRD-positive defined as BRCAm and/or genomic instability score ≥42 in the Myriad myChoice® CDx

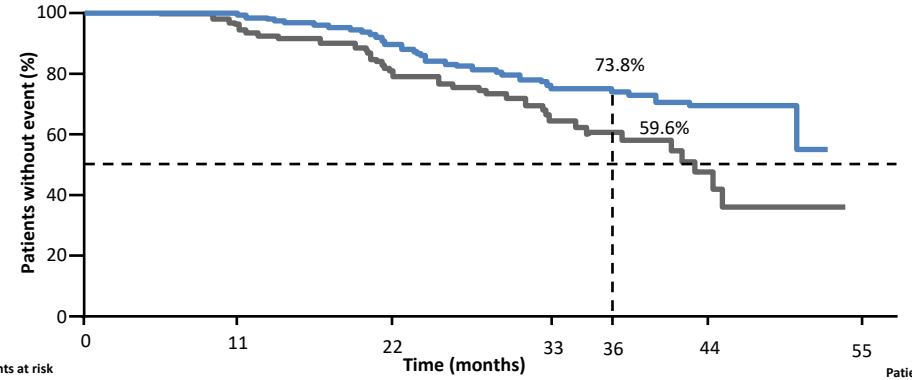
CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; PFS=progression-free survival

Pautier P, et al. Presented at ASCO Annual Meeting 2021, 4-8 June.

Olaparib + BEV resulted in PFS2 benefit regardless of FIGO stage in HRD-positive pts

Stage III

	Olaparib + bevacizumab n=182	Placebo + bevacizumab n=90
Events, n	49/182	39/90
Median PFS, months	**NR** (50.3 - NE)	**43.0** (35.3 - NE)
	HR 0.57 95% CI (0.38-0.87)	

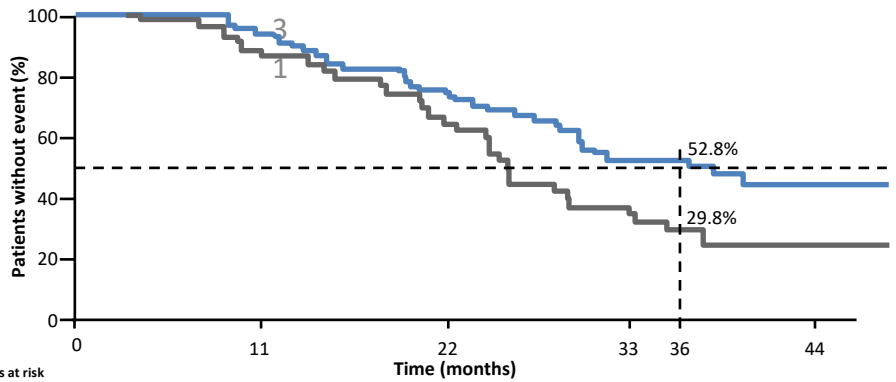


Patients at risk

Olaparib + bev	182	181	180	178	173	170	164	157	145	137	125	109	80	54	44	13	9	3	0
Placebo + bev	90	88	85	85	81	77	75	71	67	64	55	47	35	23	15	7	3	1	0

Stage IV

	Olaparib + bevacizumab n=73	Placebo + bevacizumab n=42
Events, n (%)	36/73	31/42
Median PFS, months	**37.8** (29.7 - NE)	**25.6** (22.6 - 35.2)
	HR 0.56 **95% CI (0.35-0.91)**	



Patients at risk

Olaparib + bev	73	72	72	60	65	60	59	54	50	47	35	28	22	16	10	4		
Placebo + bev	42	42	41	30	35	34	33	28	25	19	15	14	9	3	1	1		

DCO 22 March 2019.

*HRD-positive defined as BRCAm and/or genomic instability score ≥42 in the Myriad myChoice® CDx

CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; PFS=progression-free survival ; NR=not reached; PFS2=second progression-free survival

‡ Unstable median due to lack of events

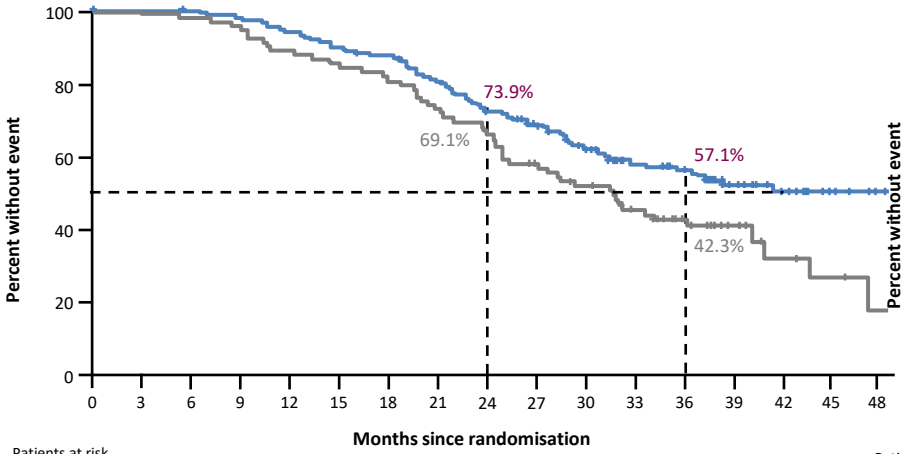
Pautier P, et al. Presented at ASCO Annual Meeting 2021, 4-8 June.

3-year PFS2 rate was >90% in HRD-positive pts who had complete resection during upfront surgery

Higher risk

Stage III with residual disease after up-surgery or who received neoadjuvant chemotherapy, Stage IV disease. Median follow-up overall 37.5 months

	Olaparib + bevacizumab n=177	Placebo + bevacizumab n=89
Events, n (%)	78 (44)	54 (60)
Median PFS2, months	**50.3**	**32.6**
	HR 0.66 95% CI 0.47–0.93	



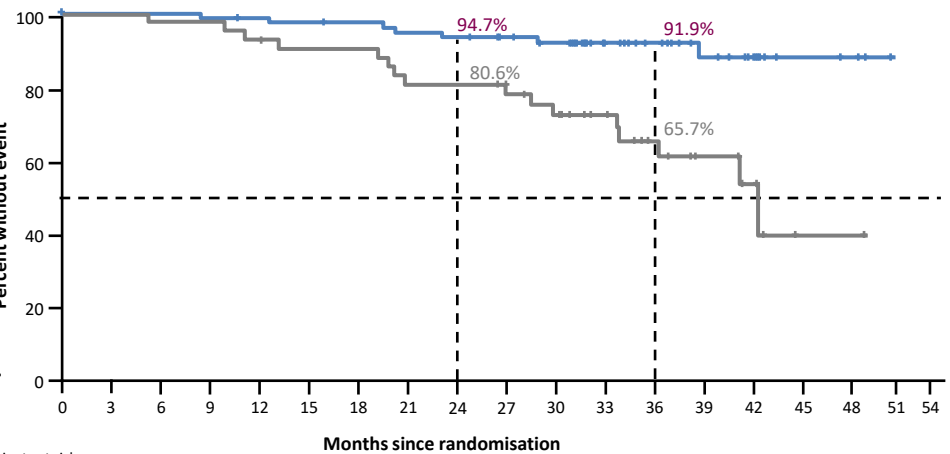
Patients at risk

Olaparib	177	175	174	170	164	156	151	140	126	116	97	81	63	42	31	10
Placebo	89	88	86	84	78	74	72	64	60	50	43	37	25	15	8	6

Lower risk

Stage III disease and complete resection following upfront surgery. Median follow-up overall 37.0 months

	Olaparib + bevacizumab n=78	Placebo + bevacizumab n=43
Events, n (%)	7 (9)	16 (37)
Median PFS2, months	**NR**	**44.3**
	HR 0.21 95% CI 0.08–0.50	



Patients at risk

Olaparib	78	78	78	77	75	74	72	71	70	68	64	56	39	28	23	7	6	3	0
Placebo	43	42	41	41	39	37	37	35	33	33	28	24	19	11	9	2	1	0	0

DCO 22 March 2020. The median time from first cycle of chemotherapy to randomization was 7 months.

*HRD-positive defined as BRCAm and/or genomic instability score ≥42 in the Myriad myChoice® CDx

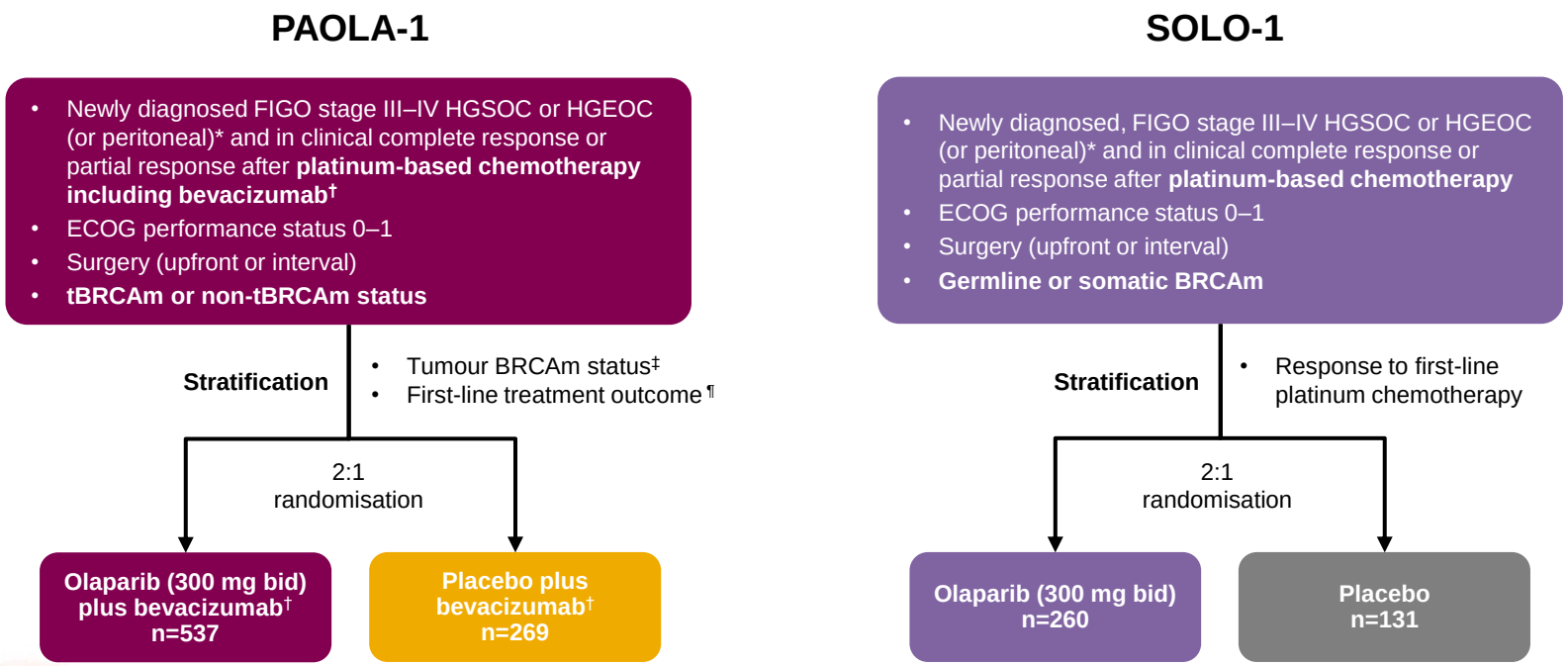
CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; NR=not reached; PFS2=second progression-free survival

Pautier P, et al. Presented at ASCO Annual Meeting 2021, 4-8 June.

Differences between PAOLA-1 and SOLO1

Study results not directly comparable without adjustment of the populations

only PTS with a BRCAm were included in SOLO-1, and a different comparator arm was used



*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation; †Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶ According to timing of surgery and NED/CR/PR
bid=twice daily; BRCAm=*BRCA1* and/or *BRCA2* mutation; CR=complete response; ECOG=Eastern Cooperative Oncology Group; FIGO=Federation of Gynecology and Obstetrics; HGEOC=high-grade endometrioid ovarian cancer; HGSOC=high-grade serous ovarian cancer; NED=no evidence of disease; PR=partial response; tBRCAm=tumour *BRCA1* and/or *BRCA2* mutation

1. Vergote I, et al. Presented at SGO Annual Conference 2020; 2. Moore K, et al. *N Engl J Med*. 2018;379(26):2495-2505; 3. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2416-2428

Population-adjusted ITC methodology

Population-adjusted ITC can estimate the relative treatment effect when comparing studies which do not have common comparator arm

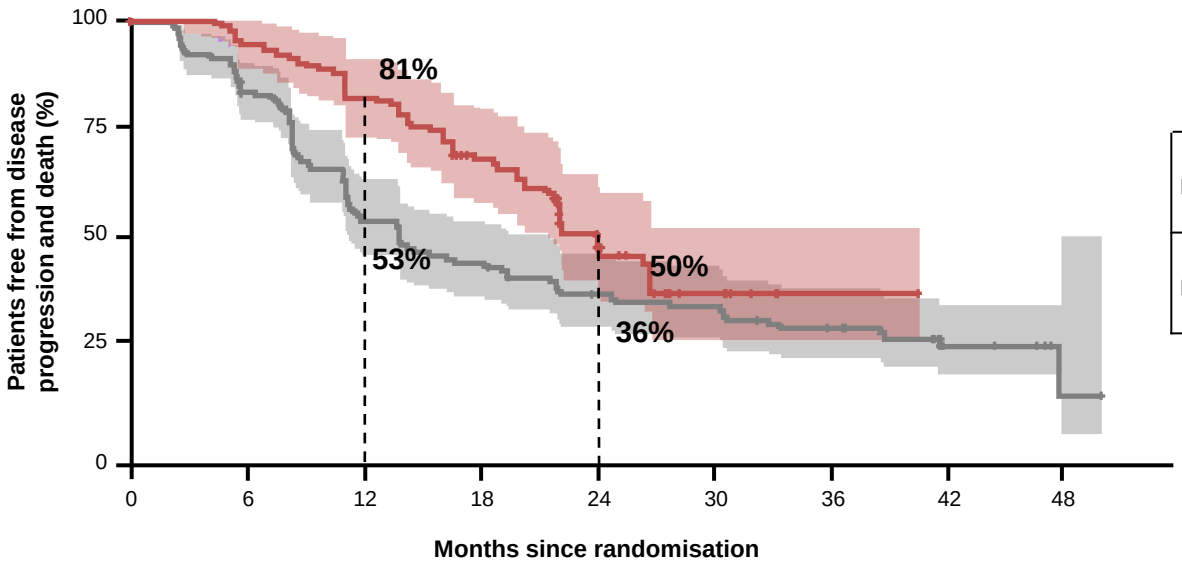
A **propensity score weighting technique** was used to minimise differences in observable characteristics between the trial populations

Weighted cox regression and Kaplan-Meier analyses were used to compare efficacy by investigator-assessed PFS (RECIST v1.1)

All analyses were performed in patients with complete baseline data.
BRCAm=mutation in *BRCA1/2*; ITC=indirect treatment comparison; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors

1. Vergote I, et al. Presented at SGO Annual Conference 2020

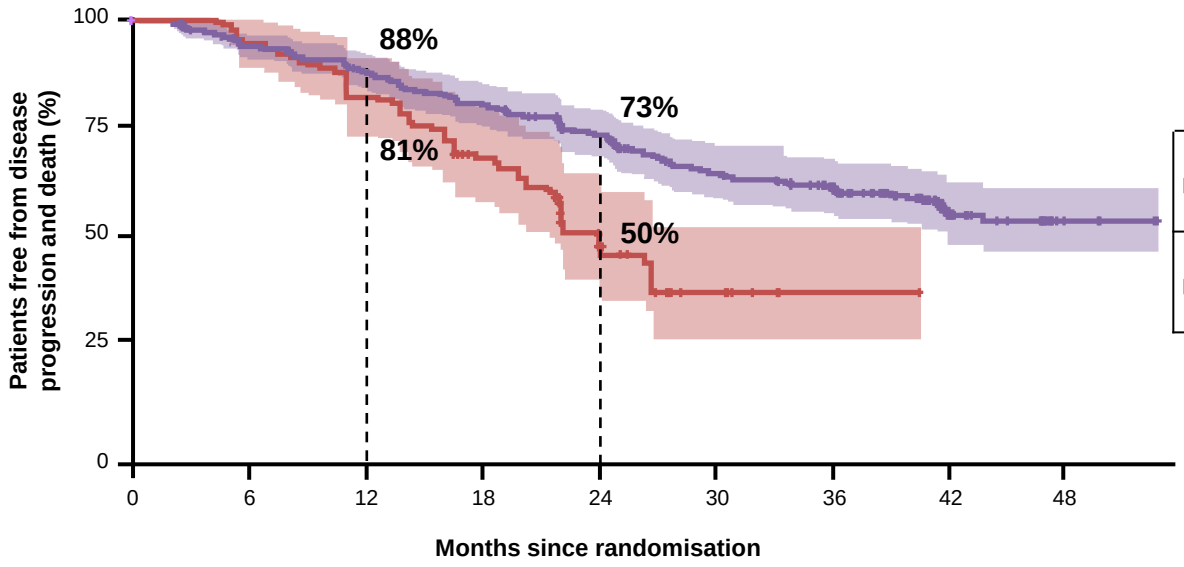
BEV monotherapy vs. placebo



	PAOLA-1 BRCAm subset	SOLO-1
	Placebo + bevacizumab* n=71	Placebo n=126
Patients progression-free at 12 months, %	81	53
Patients progression-free at 24 months, %	50	36
	HR 0.65 (95% CI 0.43–0.95)†	

*

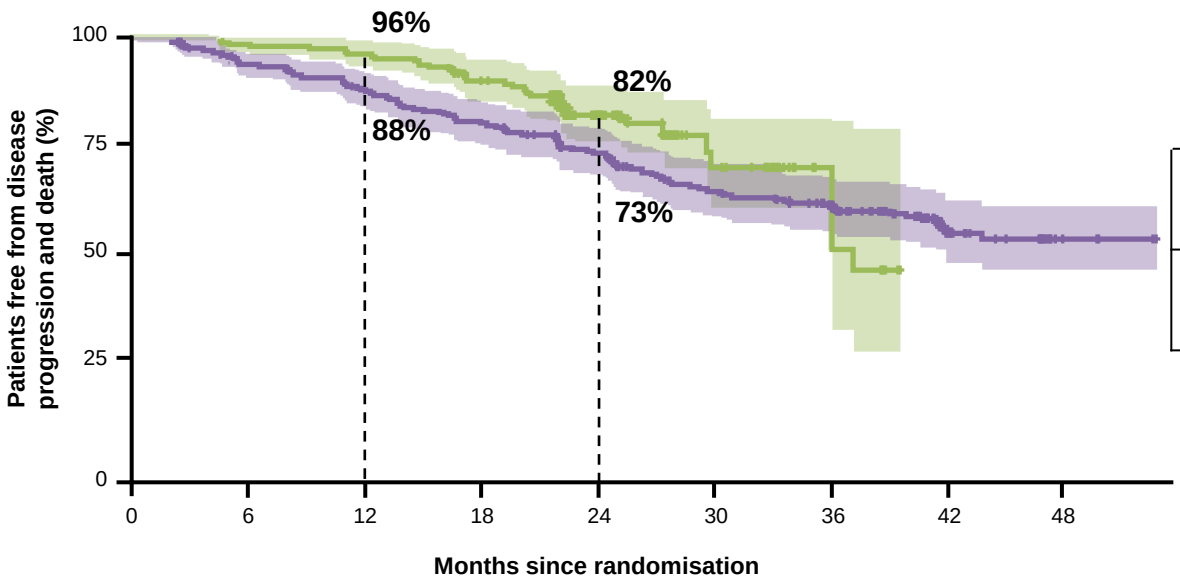
Olaparib monotherapy vs BEV monotherapy



	PAOLA-1 BRCAm subset	SOLO-1
	Placebo + bevacizumab* n=71	Olaparib n=254
Patients progression-free at 12 months, %	81	88
Patients progression-free at 24 months, %	50	73
	HR 0.48 (95% CI 0.30–0.75)†	

*

Olaparib + BEV vs Olaparib monotherapy



	PAOLA-1 BRCAm subset	SOLO-1
	Olaparib + bevacizumab* n=151	Olaparib n=254
Patients progression-free at 12 months, %	96	88
Patients progression-free at 24 months, %	82	73
	HR 0.71 (95% CI 0.45–1.09)†	

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Study Design: VELIA/GOG-3005 (NCT02470585)

Patient Population

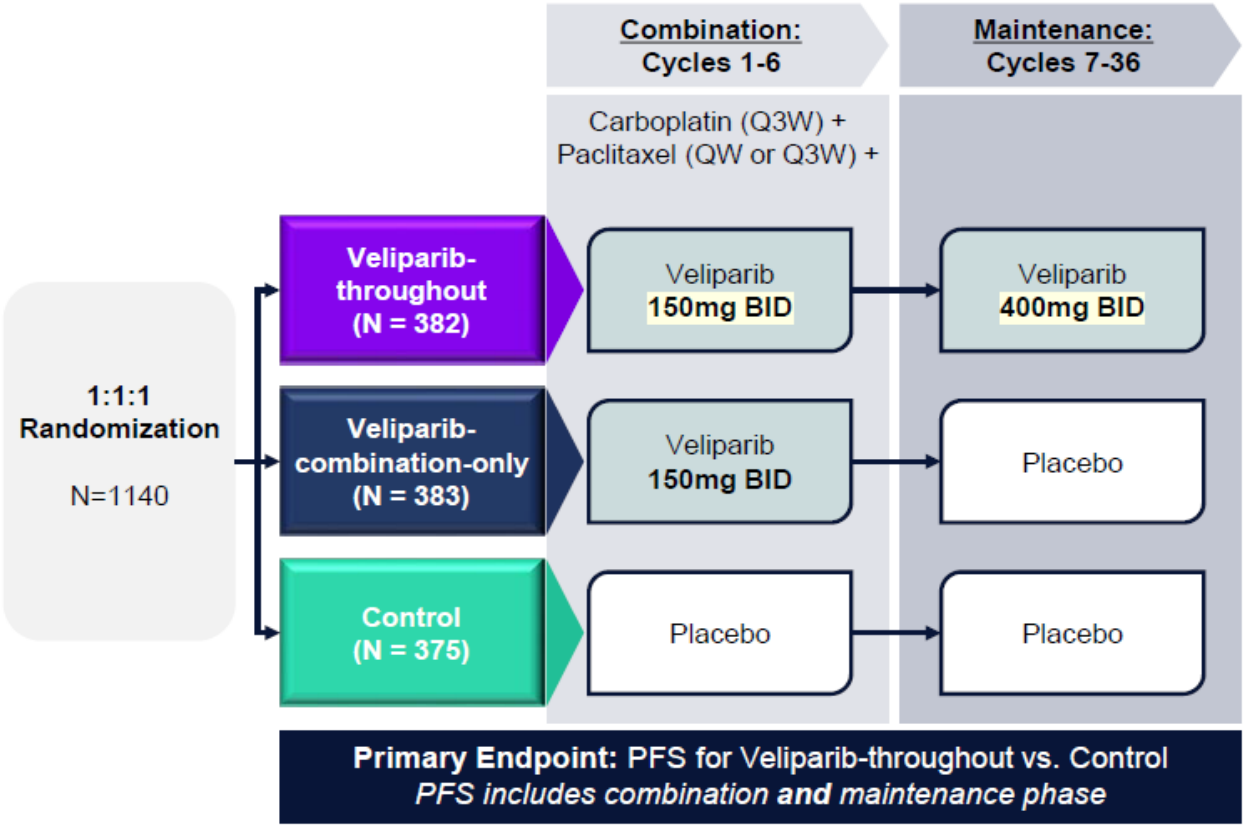
- High-Grade Serous Cancer
- FIGO Stage III or IV
- No Prior Systemic Therapy
- ECOG 0 to 2
- No CNS Metastases

Stratification Factors

- Stage of Disease
- Region
- Primary vs Interval Cytoreduction
- Residual Disease
- Chemotherapy Regimen*
- g*BRCA* Status **

* Carboplatin AUC 6 Q3W + Paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W

** Added as stratification factor ~14 months after trial initiation due to noted imbalance



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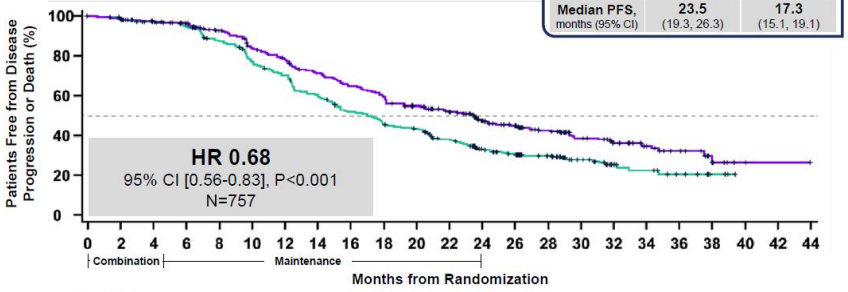
PFS by Investigator Assessment
ITT Population

BRCAm | HRD | Non-HRD

ITT	Veliparib-throughout	Control
Events (%)	191/382 (50.0)	237/375 (63.2)
Median PFS, months (95% CI)	23.5 (19.3, 26.3)	17.3 (15.1, 19.1)



No. at Risk

Control	375	356	340	328	297	260	236	202	172	153	143	119	84	70	55	36	21	16	10	3	0		
Veliparib-throughout	382	352	337	329	308	275	253	228	208	192	172	153	111	95	76	55	38	26	19	7	2	1	0

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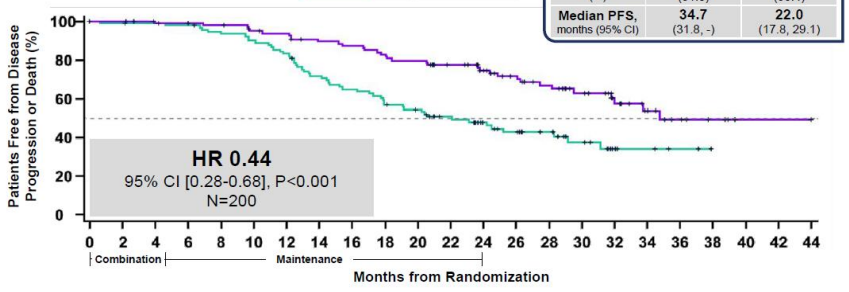
Median duration of follow-up was 28 months at the time of database lock.

PFS by Investigator Assessment
*BRCA*m Population

BRCAm | HRD | Non-HRD

BRCAm	Veliparib-throughout	Control
Events (%)	34/108 (31.5)	51/92 (55.4)
Median PFS, months (95% CI)	34.7 (31.8, -)	22.0 (17.8, 29.1)



No. at Risk

Control	92	90	89	88	84	80	74	63	57	50	46	38	29	24	19	13	6	4	2	0			
Veliparib-throughout	108	102	99	97	95	90	88	82	80	76	73	65	53	45	38	30	21	14	9	5	1	1	0

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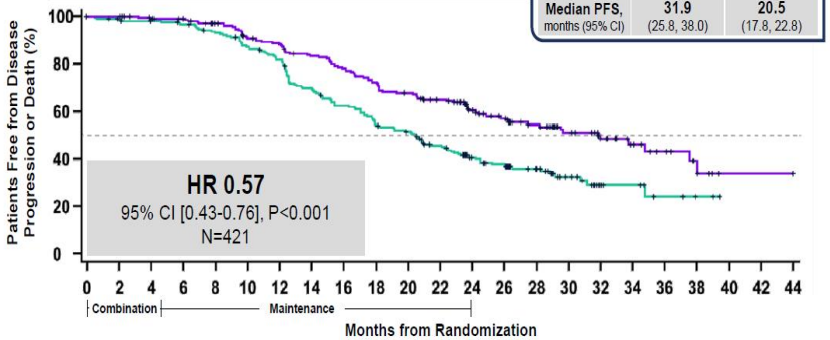
Median duration of follow-up was 28 months at the time of database lock.

PFS by Investigator Assessment
HRD Population

BRCAm | HRD | Non-HRD

HRD	Veliparib-throughout	Control
Events (%)	87/214 (40.7)	124/207 (59.9)
Median PFS, months (95% CI)	31.9 (25.8, 38.0)	20.5 (17.8, 22.8)



No. at Risk

Control	207	199	196	191	183	170	158	134	119	104	97	79	55	47	34	22	11	9	4	2	0		
Veliparib-throughout	214	203	195	191	182	167	161	150	140	130	121	109	82	72	58	44	30	19	14	5	1	1	0

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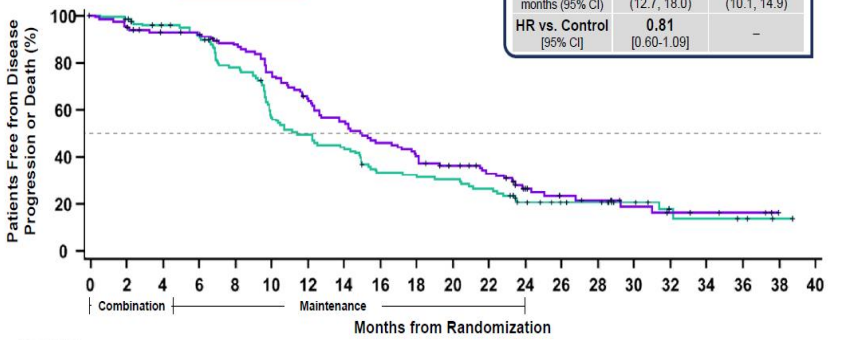
Median duration of follow-up was 28 months at the time of database lock.

PFS: Non-HRD Population

BRCAm | HRD | Non-HRD

Non-HRD *	Veliparib-throughout	Control
Median PFS, months (95% CI)	15.0 (12.7, 18.0)	11.5 (10.1, 14.9)
HR vs. Control [95% CI]	0.81 [0.60-1.09]	–



No. at Risk

Control	124	118	111	105	87	66	55	49	36	35	33	29	19	16	14	9	6	4	3	1	0		
Veliparib-throughout	125	110	103	102	94	81	68	57	48	43	35	29	18	13	11	7	5	4	3	1	0		

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* Exploratory Analysis

PARPi in 1st line of advanced EOC: ongoing trials

NCT04227522	Rucaparib Maintenance After Bevacizumab Maintenance Following CBDCA - Based First Line Chemotherapy in EOC (MAMOC)
NCT04532645	A Pan-European Non-interventional, Retrospective Observational Cohort Study of pts With BRCA Mutated FIGO Stage III-IV Ovarian Cancer Treated With Olaparib Tablets in the First-line Maintenance
NCT03462212A	Randomized, Molecular Driven Phase II Trial of CBDCA+PTX+BEV vs CBDCA + PTX + BEV + rucaparib vs CDDCA + PTX + Rucaparib, Selected According to HRD Status, in pts With Advanced (Stage III B-C-IV) Ovarian, Primary Peritoneal and Fallopian Tube Cancer (MITO 25)

Immunotherapy trials in 1st-line of EOC

NCT02718417 Randomized, Open-label, Multicenter, Phase 3 Study To Evaluate Efficacy And Safety of Avelumab in Combination with And/Or Following Chemotherapy in Pts with Previously untreated EOC (JAVELIN OVARIAN 100)

NCT03038100 A Phase III, Multicenter, Randomized, Study of Atezolizumab *vs* Placebo Administered in Combination With PTX+ CBDCA + BEV in Pts With Newly-Diagnosed Stage III-IV EOC (IMagyn050)

Immunotherapy trials in 1st-line of EOC

NCT03740165	Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA Non-mutated Advanced EOC (KEYLYNK-001 / ENGOT-ov43 / GOG-3036
NCT03522246	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in EOC Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based CT (ATHENA) (rucaparib + nivolumab, rucaparib+ placebo, oral placebo+ nivolumab, oral placebo + IV placebo)

Available 1st-line maintenance therapy options

	Niraparib	Olaparib	Olaparib + Bevacizumab	Bevacizumab
	All comers	BRCAm	BRCAm or HRD	All comers
	All comers	BRCAm	BRCAm or HRD	All comers

Algorithm for 1st line of advanced EOC

- ✓ All pts start treatment with the first cycle of q3w PTX 175 mg/m^2 + CBDCA AUC5 regimen.
- ✓ The results of BRCA testing on tissue samples collected at PDS or laparoscopy or CT/US- guided biopsies should be available before the second cycle
- ✓ **BRCA mutated**: PTX/CBDCA followed by olaparib maintenance in responsive cases according to SOLO1 trial [HR=0.33].
- ✓ **BRCA wild-type**: Clinical behavior depends on both the availability of HRD assay as well as by the presence or lack of risk factors for BEV- related AE

Algorithm for 1st line of advanced BRCA-wt EOC

Not available HRD assay

- ✓ **No contraindications to BEV:** BEV can be added concurrently PTX/CBDCA and sequentially as maintenance according to GOG 218
- ✓ **Contraindications to BEV:** PTX/CBDCA eventually followed by niraparib according to PRIMA (niraparib →absolute median PFS benefit of 5.6 months [HR=0.62] in ITT population)

Algorithm for 1st line of advanced BRCA-wt EOC

Positive HRD assay

- ✓ No contraindications to BEV: BEV can be added concurrently to PTX/CBDCA and then sequentially and olaparib can be added as maintenance according to PAOLA-1(Olaparib + BEV→ median absolute PFS benefit of 11.5 mos [HR=0.43] *vs* PL+BEV in pts with HRD and BRCA-wt
- ✓ Contraindications to BEV: PTX/CBDCA followed by niraparib according to PRIMA (niraparib→ absolute median PFS benefit of 11.4 months [HR=0.50] *vs* PL in pts with HRD and BRCA-wt)

Algorithm for 1st line of advanced BRCA-wt EOC

Negative HRD assay

- ✓ No contraindications to BEV: BEV can be added concurrently to PTX/CBDCA and then sequentially as maintenance [according to GOG218]
- ✓ Contraindications to BEV: PTX/CBDCA eventually followed by niraparib according to PRIMA (Niraparib → absolute median PFS benefit of 2.7 months only [HR=0.68) *vs* PL in pts with HRP)
- ✓ The role of immunotherapy in first line treatment is still investigational