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Efficacy of maintenance olaparib plus bevacizumab by biomarker status in clinical higher- and lower-risk patients with newly diagnosed, advanced ovarian cancer in the PAOLA-1/ENGOT-ov25 trial

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Introduction

- Although all patients with newly diagnosed, advanced ovarian cancer are at high risk for disease progression, factors such as disease stage and the quality of surgical outcome impact their risk of relapse and survival[1]
- The Phase III PAOLA-1/ENGOT-ov25 trial evaluated the addition of maintenance olaparib to bevacizumab in women with advanced, high-grade ovarian cancer who were in response* after first-line platinum-based chemotherapy plus bevacizumab:[2]
  - Adding maintenance olaparib to bevacizumab improved investigator-assessed PFS, compared with placebo plus bevacizumab, in the ITT population (HR 0.59; 95% CI 0.49–0.72)
- Patient selection in PAOLA-1 was not restricted by surgical outcome:
  - We conducted exploratory subgroup analyses evaluating investigator-assessed PFS in two clinical subgroups (**higher-risk** patients: FIGO stage III disease with upfront surgery and residual disease or NACT, or FIGO stage IV disease; **lower-risk** patients: FIGO stage III disease with upfront surgery and complete resection) including by biomarker status

*NED (defined as no measurable/assessable disease after upfront or interval cytoreductive surgery plus no radiologic evidence of disease and a normal CA-125 level after chemotherapy), clinical CR (defined as the disappearance of all measurable/assessable disease and normalization of CA-125 levels) or clinical PR (defined as radiologic evidence of disease and/or an abnormal CA-125 level)
CI, confidence interval; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; HR hazard ratio; ITT, intent to treat; NACT, neoadjuvant chemotherapy; NED, no evidence of disease; PR, partial response; PFS, progression-free survival

1. du Bois A *et al. Cancer* 2009;115:1234–44; 2. Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28

PAOLA-1/ENGOT-ov25 study design

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

First-line treatment:
- Upfront or interval surgery
- Platinum-taxane based chemotherapy
- ≥2 cycles of bevacizumab†

NED/CR/PR

Maintenance therapy

Olaparib tablets 300 mg bid x 2 years
+ bevacizumab‡

2:1 randomization stratified by:
- Tumour BRCAm status¶
- First-line treatment outcome§

Placebo x 2 years
+ bevacizumab‡

Primary endpoint
Investigator-assessed PFS (RECIST v1.1)

Secondary endpoints
TFST, PFS2, TSST, OS
HRQoL
Safety and tolerability

Exploratory investigator-assessed PFS analyses
Higher-risk patients:
- FIGO stage III patients with upfront surgery and residual disease or NACT
- FIGO stage IV patients

Lower-risk patients:
- FIGO stage III patients with upfront surgery and complete resection

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation; †Patients must have received ≥3 cycles of bevacizumab, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; ‡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; CR, complete response; BRCAm, BRCA mutation; HRQoL, health-related quality of life; NED, no evidence of disease; OS, overall survival; PFS2, time to second progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Patient characteristics

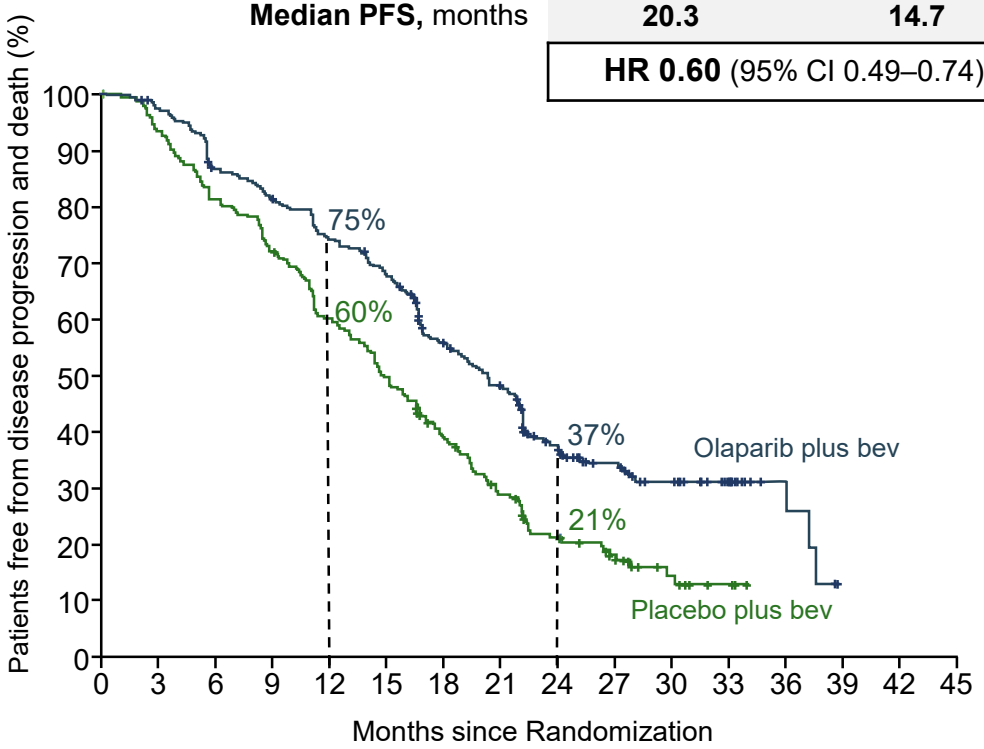
	Higher-risk subgroup		Lower-risk subgroup	
	Olaparib + bev (n=399)	Placebo + bev (n=196)	Olaparib + bev (n=138)	Placebo + bev (n=73)
Median age, years	62	61	59	56
Upfront surgery, n (%) Macroscopic residual disease Complete resection	133 (33) 111 (83) 22* (17)	65 (33) 53 (82) 12* (18)	138 (100) – 138 (100)	73 (100) – 73 (100)
Interval surgery, n (%) Macroscopic residual disease Complete resection	228 (57) 65 (29) 163 (71)	110 (56) 35 (32) 75 (68)	0 – –	0 – –
No surgery, n (%)	38 (10)	21 (11)	0	0
Response after first-line therapy, n (%) NED/Clinical CR Clinical PR	 259 (65) 140 (35)	 123 (63) 73 (37)	 137 (99) 1 (1)	 71 (97) 2 (3)
Normal serum CA-125 level, n (%)† Yes No	 333 (83) 66 (17)	 165 (84) 30 (15)	 130 (94) 8 (6)	 69 (95) 4 (5)
Deleterious tumour BRCAm, n (%) Yes No	 109 (27) 290 (73)	 55 (28) 141 (72)	 48 (35) 90 (65)	 25 (34) 48 (66)
Myriad tumour HRD status, n (%) HRD positive‡ HRD negative/unknown§	 177 (44) 222 (56)	 89 (45) 107 (55)	 78 (57) 60 (43)	 43 (59) 30 (41)

*Patients with stage IV disease; †Missing data for one higher-risk patient (1%) in the olaparib plus bevacizumab group; ‡HRD positive was defined as a tumour BRCAm or a genomic instability score of ≥42 on the Myriad myChoice CDx® assay; §HRD negative was defined as a genomic instability score of <42 and unknown was defined as an inconclusive, missing or failed test
bev, bevacizumab; HRD, homologous recombination deficiency

PFS by clinical risk*

Higher risk

	Olaparib + bev (n=399)	Placebo + bev (n=196)
Events, n (%)	239 (60)	154 (79)
Median PFS, months	**20.3**	**14.7**
HR 0.60 (95% CI 0.49–0.74)		



Number of patients at risk:

Olaparib plus bev	399	381	336	313	287	259	188	153	86	68	31	19	6	0
Placebo plus bev	196	180	157	139	114	95	67	48	31	21	9	4	0	

*The median time from the first cycle of chemotherapy to randomization was 7 months. The median duration of follow-up for PFS in higher-risk patients was 22.3 months (olaparib plus bevacizumab) and 24.6 months (placebo plus bevacizumab)

PFS by clinical risk*

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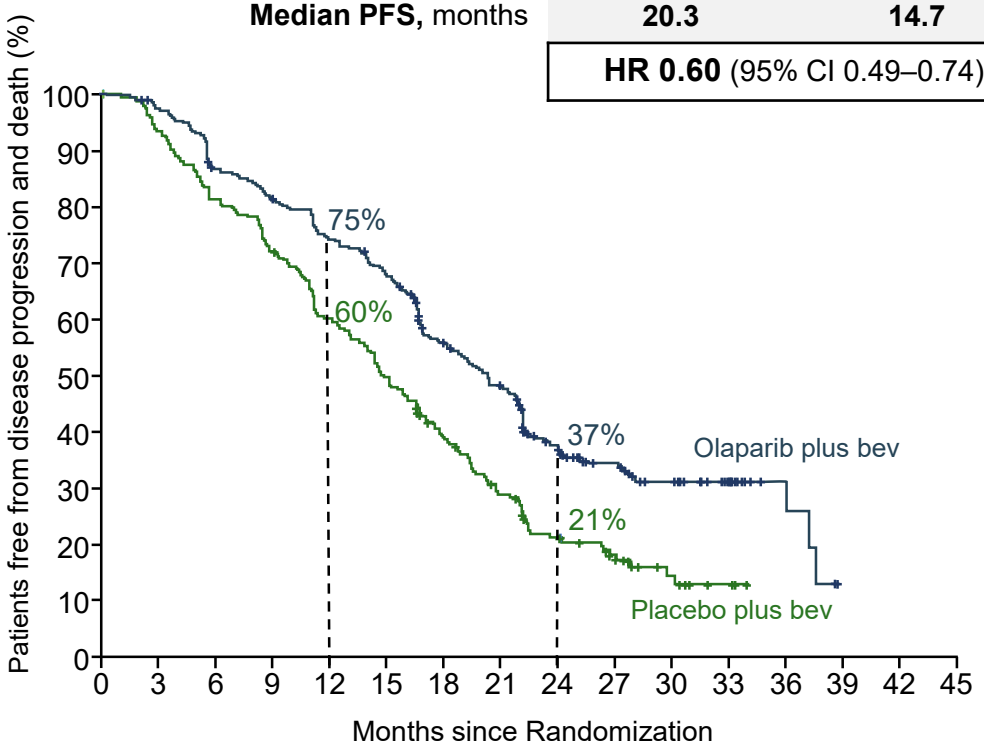
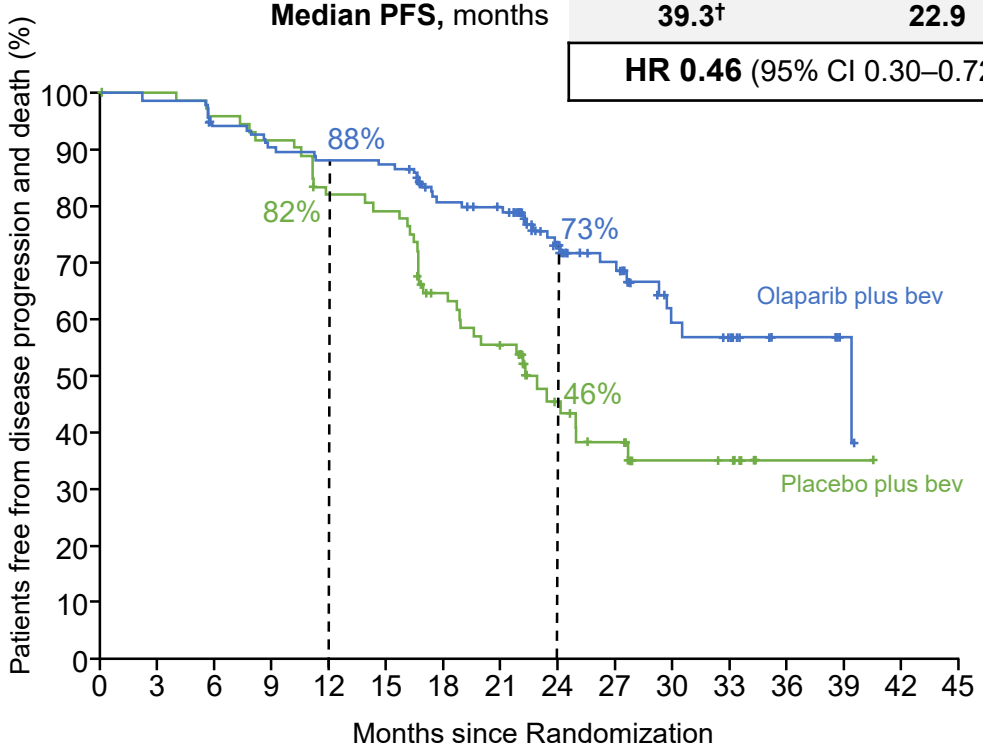


Number of patients at risk:

Olaparib plus bev	399	381	336	313	287	259	188	153	86	68	31	19	6	0
Placebo plus bev	196	180	157	139	114	95	67	48	31	21	9	4	0	

Lower risk

	Olaparib + bev (n=138)	Placebo + bev (n=73)
Events, n (%)	41 (30)	40 (55)
Median PFS, months	**39.3†**	**22.9**
HR 0.46 (95% CI 0.30–0.72)		



Number of patients at risk:

Olaparib plus bev	138	132	125	120	116	115	91	87	55	44	24	18	6	3	0
Placebo plus bev	73	72	69	66	58	56	42	35	19	14	6	5	1	1	0

*The median time from the first cycle of chemotherapy to randomization was 7 months. The median duration of follow-up for PFS in higher-risk patients was 22.3 months (olaparib plus bevacizumab) and 24.6 months (placebo plus bevacizumab) and in lower-risk patients was 23.9 months (olaparib plus bevacizumab) and 22.3 months (placebo plus bevacizumab)

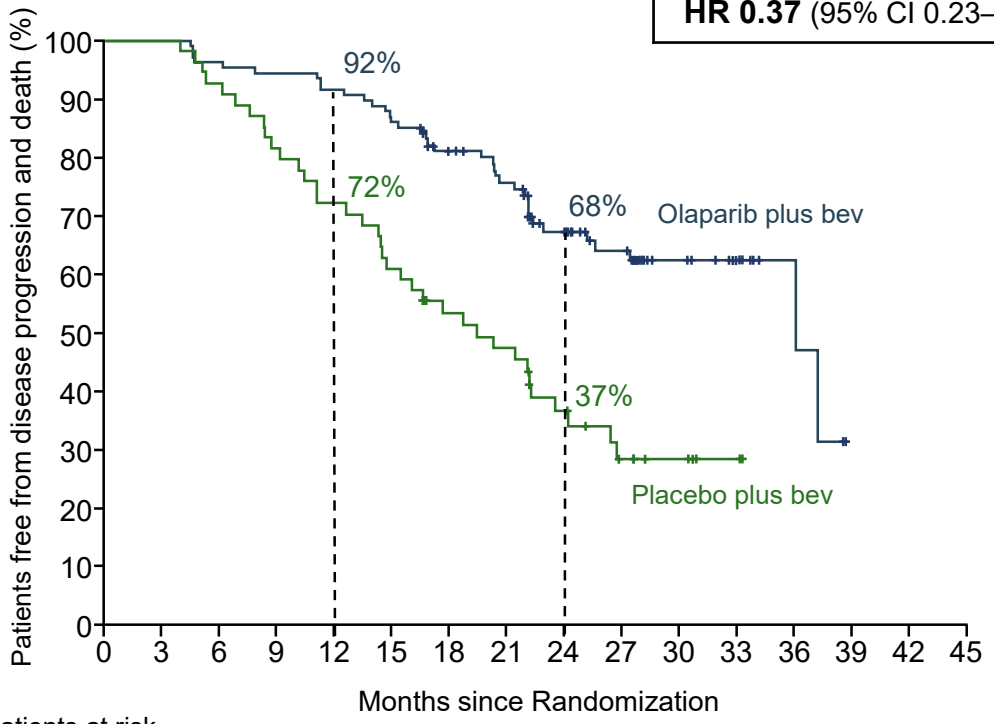
†Unstable median due to lack of events

PFS by clinical risk in tumour BRCAm patients

Higher risk, tumour BRCAm

	Olaparib + bev (n=109)	Placebo + bev (n=55)
Events, n (%)	37 (34)	36 (65)
Median PFS, months	**36.0***	**19.4**

HR 0.37 (95% CI 0.23–0.59)



Number of patients at risk:

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

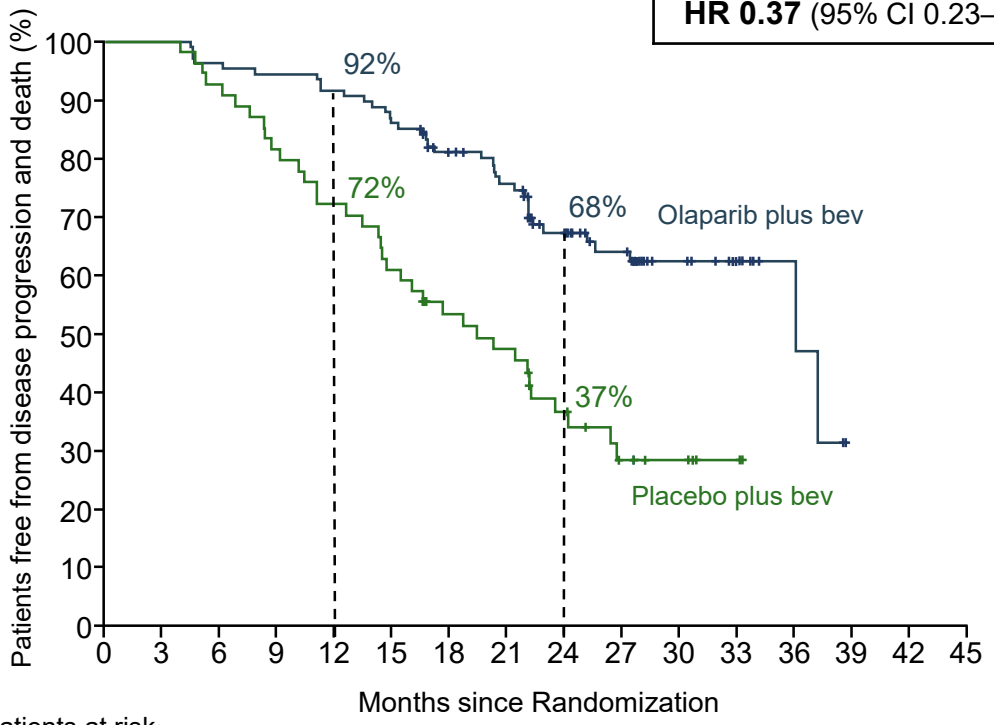
*Unstable median due to lack of events

PFS by clinical risk in tumour BRCAm patients

Higher risk, tumour BRCAm

	Olaparib + bev (n=109)	Placebo + bev (n=55)
Events, n (%)	37 (34)	36 (65)
Median PFS, months	**36.0***	**19.4**

HR 0.37 (95% CI 0.23–0.59)



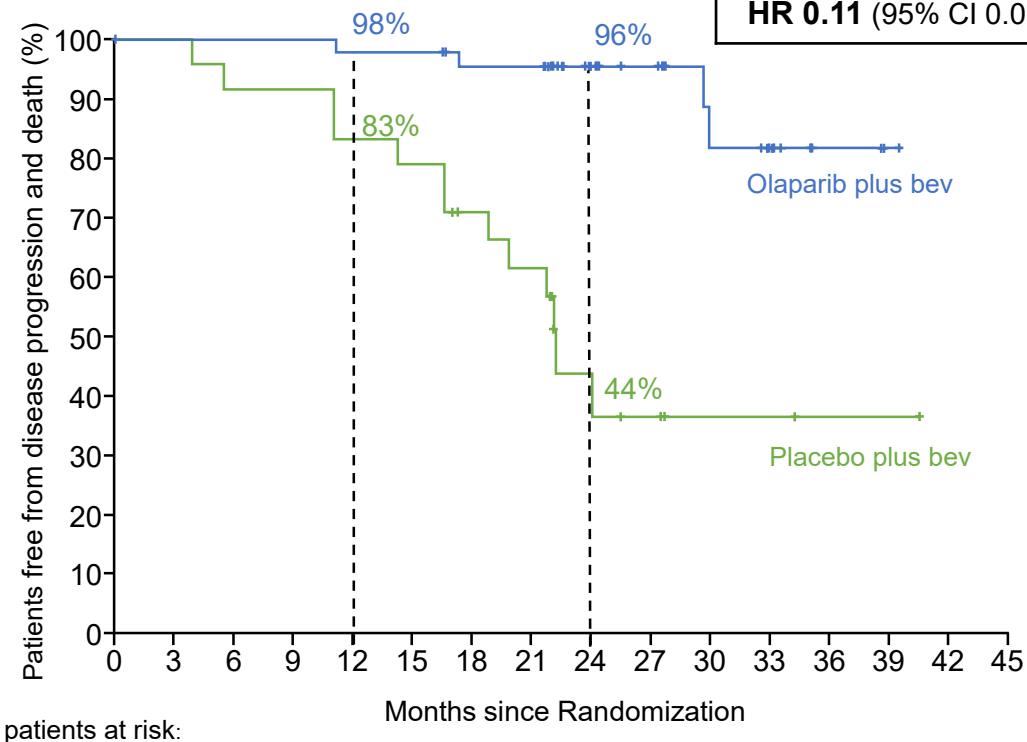
Number of patients at risk:

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

Lower risk, tumour BRCAm

	Olaparib + bev (n=48)	Placebo + bev (n=25)
Events, n (%)	4 (8)	13 (52)
Median PFS, months	**NR**	**22.2**

HR 0.11 (95% CI 0.03–0.31)



Number of patients at risk:

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

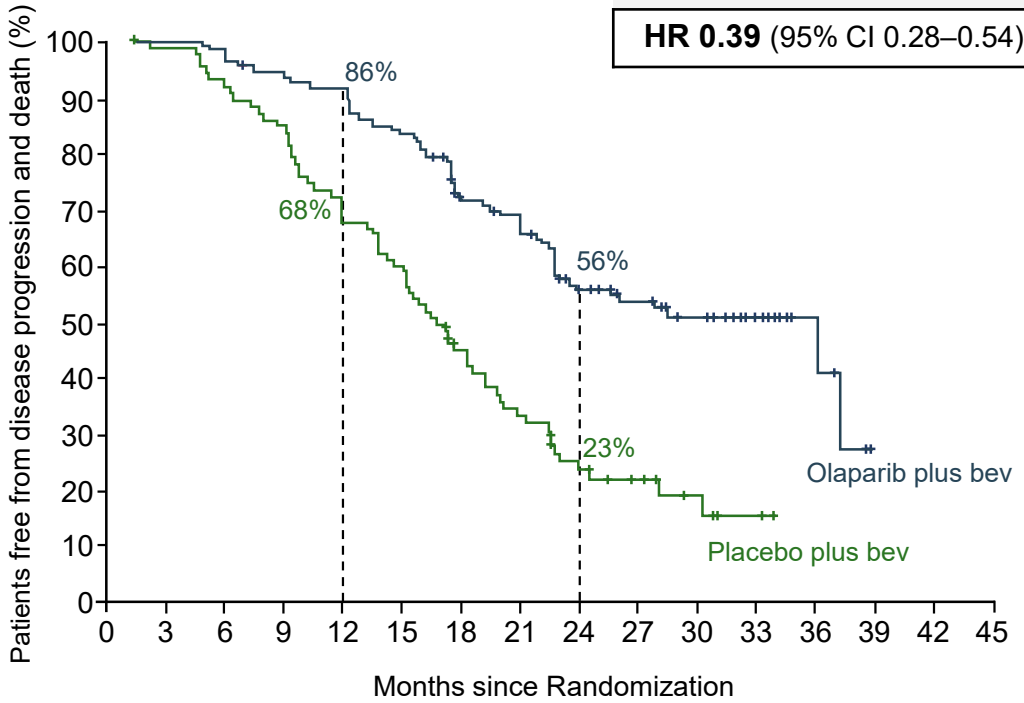
*Unstable median due to lack of events
NR, not reached

PFS by clinical risk in HRD-positive patients

Higher risk, HRD positive

	Olaparib + bev (n=177)	Placebo + bev (n=89)
Events, n (%)	77 (44)	67 (75)
Median PFS, months	**36.0***	**16.0**

HR 0.39 (95% CI 0.28–0.54)



Number of patients at risk:

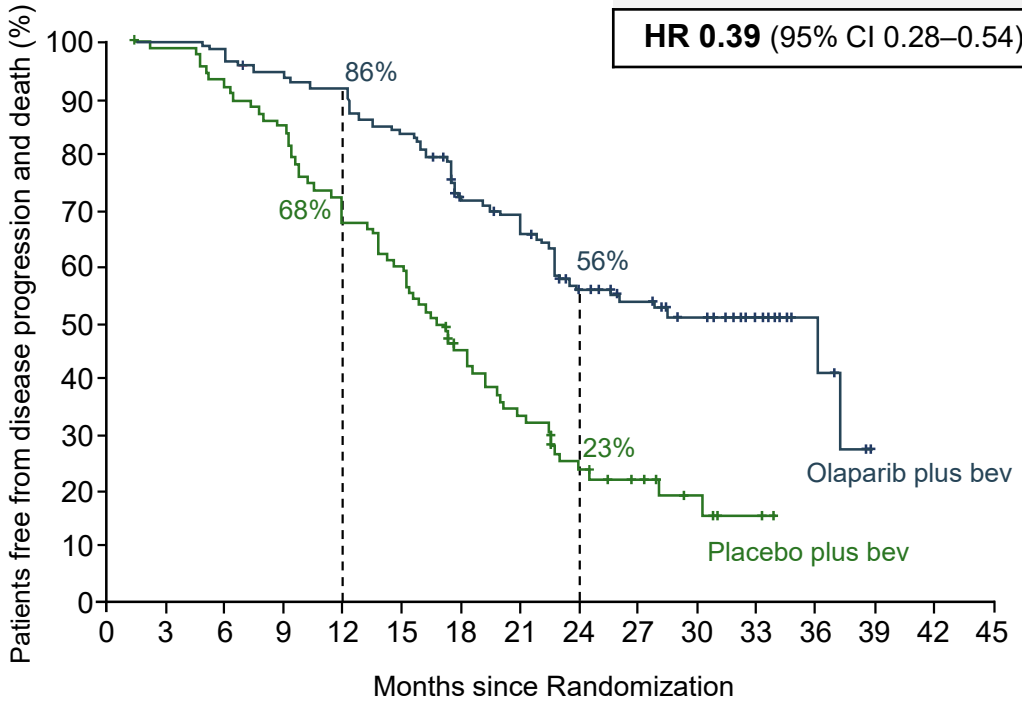
Olaparib plus bev	177	175	166	161	150	140	109	95	63	50	27	15	5	0	0
Placebo plus bev	89	86	78	66	59	47	31	24	16	11	5	2	0	0	0

*Unstable median due to lack of events

PFS by clinical risk in HRD-positive patients

Higher risk, HRD positive

	Olaparib + bev (n=177)	Placebo + bev (n=89)
Events, n (%)	77 (44)	67 (75)
Median PFS, months	**36.0***	**16.0**
HR 0.39 (95% CI 0.28–0.54)		

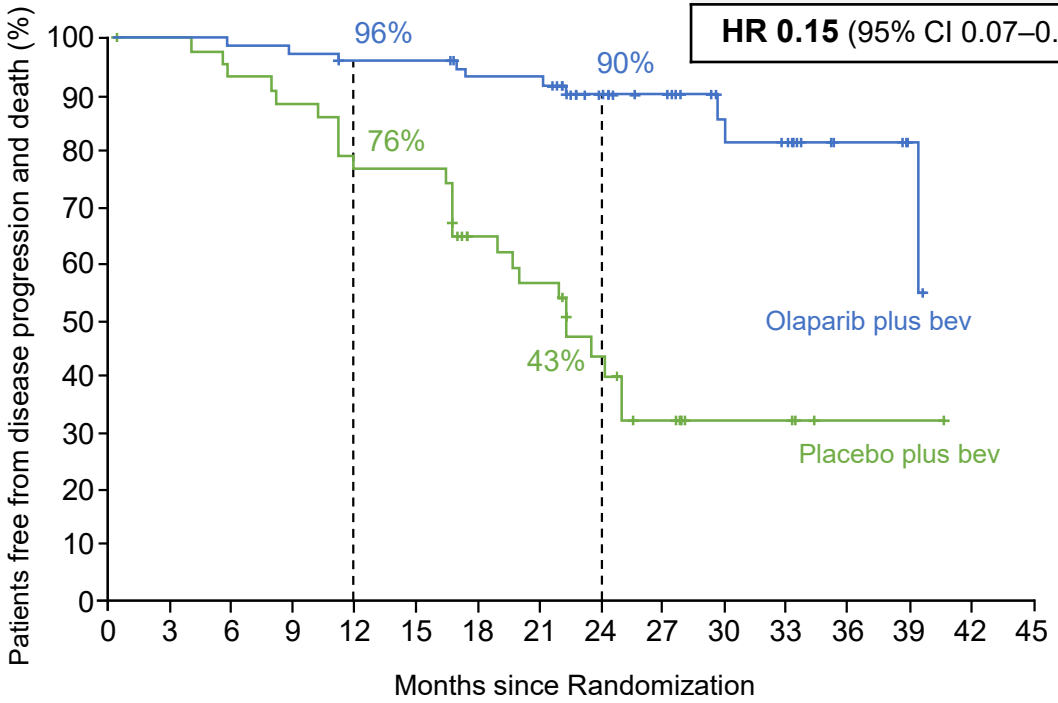


Number of patients at risk:

Olaparib plus bev	177	175	166	161	150	140	109	95	63	50	27	15	5	0	0
Placebo plus bev	89	86	78	66	59	47	31	24	16	11	5	2	0	0	0

Lower risk, HRD positive

	Olaparib + bev (n=78)	Placebo + bev (n=43)
Events, n (%)	10 (13)	25 (58)
Median PFS, months	**NR**	**22.1**
HR 0.15 (95% CI 0.07–0.30)		



Number of patients at risk:

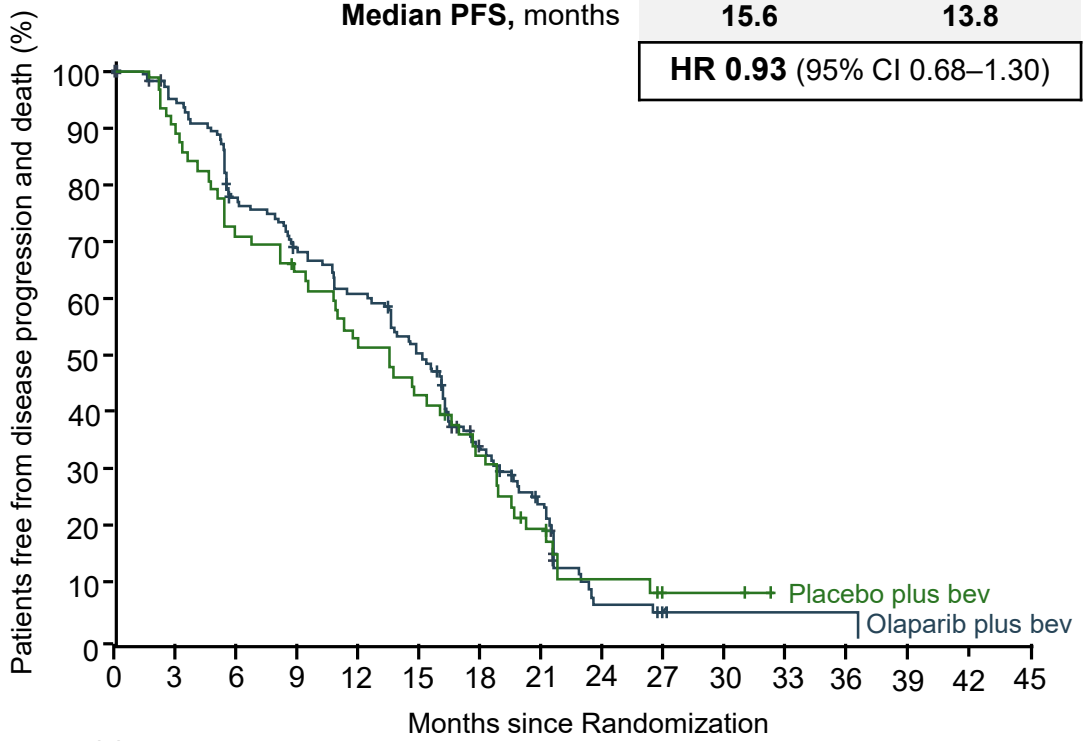
Olaparib plus bev	78	77	76	75	73	73	60	60	40	35	19	14	6	3	0
Placebo plus bev	43	42	39	37	32	32	23	20	12	7	3	3	1	1	0

*Unstable median due to lack of events

PFS by clinical risk in HRD-negative patients*

Higher risk, HRD negative

	Olaparib + bev (n=144)	Placebo + bev (n=62)
Events, n (%)	117 (81)	53 (85)
Median PFS, months	**15.6**	**13.8**
HR 0.93 (95% CI 0.68–1.30)		



No. of patients at risk

Olaparib plus bev	144	132	106	93	82	69	42	28	7	5	1	1	1	0
Placebo plus bev	62	56	45	41	32	28	20	10	5	5	2	1	0	

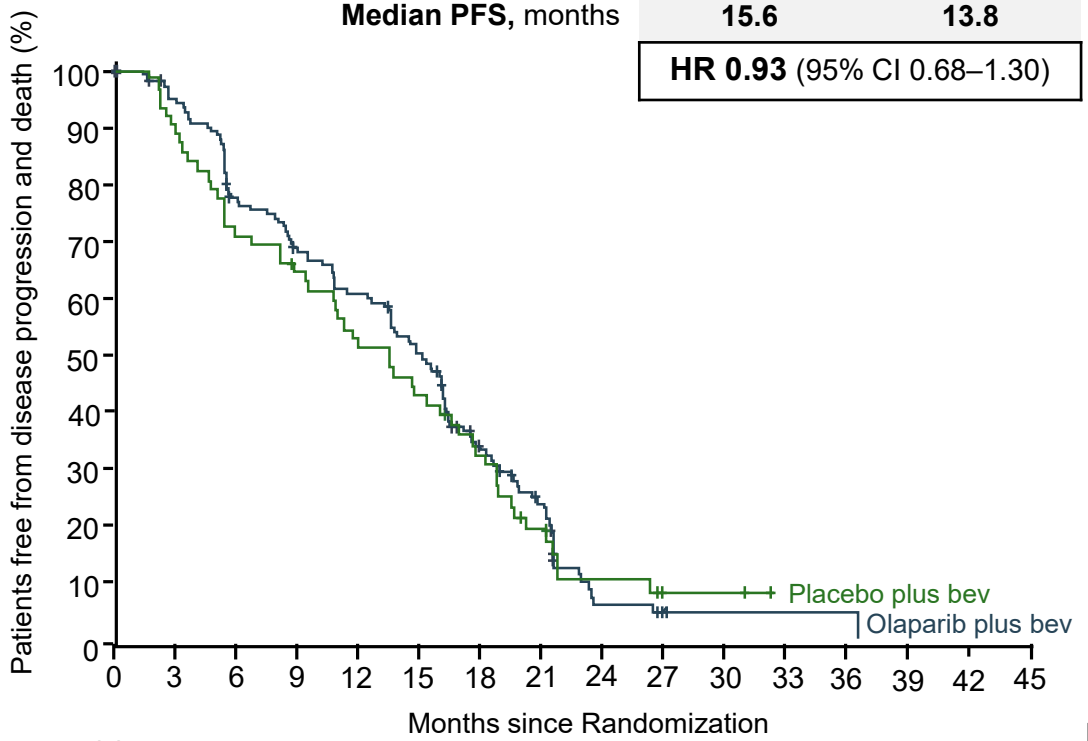
*In the remaining subgroup of HRD-unknown patients, median PFS was 19.8 months with olaparib plus bevacizumab (n=78) vs 14.3 months with placebo plus bevacizumab (n=45) in higher-risk patients (HR 0.63; 95% CI 0.41–1.00)

PFS by clinical risk in HRD-negative patients*

Higher risk, HRD negative

	Olaparib + bev (n=144)	Placebo + bev (n=62)
Events, n (%)	117 (81)	53 (85)
Median PFS, months	**15.6**	**13.8**

HR 0.93 (95% CI 0.68–1.30)



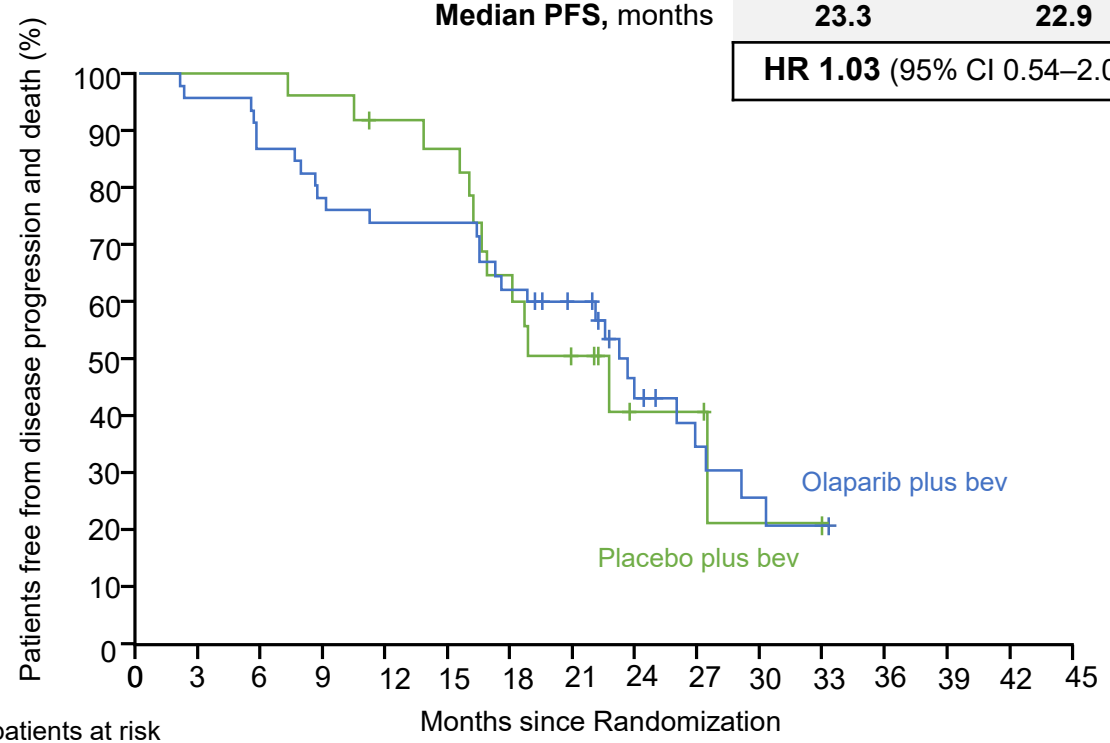
No. of patients at risk

Olaparib plus bev	144	132	106	93	82	69	42	28	7	5	1	1	1	0
Placebo plus bev	62	56	45	41	32	28	20	10	5	5	2	1	0	

Lower risk, HRD negative

	Olaparib + bev (n=48)	Placebo + bev (n=23)
Events, n (%)	28 (58)	13 (57)
Median PFS, months	**23.3**	**22.9**

HR 1.03 (95% CI 0.54–2.06)



No. of patients at risk

Olaparib plus bev	48	43	39	35	33	33	25	21	13	8	5	4	0	
Placebo plus bev	23	23	23	22	20	19	14	10	3	3	1	1	0	

*In the remaining subgroup of HRD-unknown patients, median PFS was 19.8 months with olaparib plus bevacizumab (n=78) vs 14.3 months with placebo plus bevacizumab (n=45) in higher-risk patients (HR 0.63; 95% CI 0.41–1.00), and was NR with olaparib plus bevacizumab (n=12) and NR with placebo plus bevacizumab (n=7) in lower-risk patients (HR 1.46; 95% CI 0.24–11.15)

Conclusions

- In PAOLA-1, maintenance olaparib plus bevacizumab provided a PFS benefit over bevacizumab alone in both the higher-risk and lower-risk subgroups:
  - The reduction in the risk of disease progression or death was 40% in higher-risk patients and 54% in lower-risk patients
  - Median PFS increased from 14.7 months with bevacizumab alone to 20.3 months with the combination of olaparib plus bevacizumab in higher-risk patients and from 22.9 months to 39.3* months in lower-risk patients
- Consistent with the overall PAOLA-1 population, olaparib plus bevacizumab provided the greatest PFS benefit over placebo plus bevacizumab in **higher- and lower-risk** patients who were HRD positive or who had a tumour BRCAm
- The substantial PFS improvement seen with olaparib plus bevacizumab in **lower-risk** patients with a tumour BRCAm or who were HRD positive, with 2-year PFS rates of ≥90%, raises the hope of long-term benefit or even cure

*Unstable median due to lack of events

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