PARIS 2022 ESMO congress

Final overall survival results from the Phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer

Isabelle Ray-Coquard,[1] Alexandra Leary,[2] Sandro Pignata,[3] Claire Cropet,[4] Antonio González-Martín,[5] Gerhard Bogner,[6] Hiroyuki Yoshida,[7] Ignace Vergote,[8] Nicoletta Colombo,[9] Johanna Mäenpää,[10] Frédéric Selle,[11] Barbara Schmalfeldt,[12] Giovanni Scambia,[13] Eva Maria Guerra Alia,[14] Claudia Lefeuvre-Plesse,[15] Antje Belau,[16] Alain Lortholary,[17] Martina Gropp-Meier,[18] Eric Pujade-Lauraine,[19] Philipp Harter[20]

[1]Centre Léon BERARD, Lyon, and GINECO, France; [2]Institut Gustave Roussy, Villejuif, and GINECO, France; [3]Istituto Nazionale Tumori 'Fondazione G Pascale', IRCCS, Napoli, and MITO, Italy; [4]Centre Léon BERARD, Lyon,, France; [5]Clínica Universidad de Navarra, Madrid, and GEICO, Spain; [6]Paracelsus Medical University Salzburg, Salzburg, and AGO Au, Austria; [7]Saitama Medical University International Medical Center, Saitama, and GOTIC, Japan; [8]Leuven Cancer Institute, Leuven, and BGOG, Belgium; [9]European Institute of Oncology, Milan, and MANGO, Italy; [10]Tampere University and University Hospital, Tampere, and NSGO, Finland; [11]Groupe Hospitalier Diaconesses Croix Saint-Simon, Paris, and GINECO, France; [12]Universitätsklinikum Hamburg-Eppendorf, Hamburg, and AGO, Germany; [13]Università Cattolica del Sacro Cuore di Roma, Rome, and MITO, Italy; [14]Hospital Universitario Ramón y Cajal, Madrid, and GEICO, Spain; [15]Centre Eugène Marquis, Rennes, and GINECO, France; [16]Universitätsmedizin Greifswald, Frauenklinik & Frauenarztpraxis, Greifswald, and AGO, Germany; [17]Hopital privé du Confluent, Nantes, and GINECO, France; [18]Onkologie Ravensburg, Ravensburg, and AGO, Germany; [19]ARCAGY Research, Paris, France; [20]Kliniken Essen-Mitte, Essen, and AGO, Germany

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DECLARATION OF INTERESTS

- **Isabelle Ray-Coquard** reports honoraria (self) from Abbvie, Agenus, Advaxis, BMS, PharmaMar, Genmab, Pfizer, AstraZeneca, Roche, GSK, MSD, Deciphera, Mersena, Merck Sereno, Novartis, Amgen, Tesaro and Clovis; honoraria (institution) from GSK, MSD, Roche and BMS; advisory/consulting fees from Abbvie, Agenus, Advaxis, BMS, PharmaMar, Genmab, Pfizer, AstraZeneca, Roche/Genentech, GSK, MSD, Deciphera, Mersena, Merck Sereno, Novartis, Amgen, Tesaro and Clovis; research grant/funding (self) from MSD, Roche and BMS; research grant/funding (institution) from MSD, Roche, BMS, Novartis, Astra Zeneca and Merck Sereno; and travel support from Roche and AstraZeneca and GSK
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- **Claire Cropet** has no potential conflicts of interest
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- **Martina Gropp-Meier** reports no disclosures
- **Eric Pujade-Lauraine** reports lecture fees, speaker's bureau fees, and travel support from AstraZeneca, Tesaro, and Roche, lecture fees from Clovis Oncology, Incyte, and Pfizer and is employed by ARCAGY Research
- **Philipp Harter** reports honoraria from AstraZeneca, Roche, Clovis Oncology, Stryker, MSD Oncology, Zai Lab, Lilly, Sotio, Esai, GlaxoSmithKline; consulting/advisory roles from AstraZeneca, Roche, Tesaro, Merck, GlaxoSmithKline, Clovis Oncology, Immunogen; and research funding (inst) from AstraZeneca, Roche, Genmab, GlaxoSmithKline, Immunogen, and Clovis Oncology

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Background

- The Phase III PAOLA-1/ENGOT-ov25 trial compared the efficacy of maintenance olaparib + bevacizumab with placebo + bevacizumab in patients with newly diagnosed advanced ovarian cancer who had received first-line standard-of-care treatment including bevacizumab

- In the primary analysis, olaparib + bevacizumab demonstrated a significant PFS benefit over placebo + bevacizumab (HR 0.59, 95% CI 0.49–0.72; *P*<0.001),[1] mainly in patients with HRD-positive* tumours (HR 0.33, 95%CI 0.25–0.45)[1]

- This final PAOLA-1 analysis investigates whether the PFS advantage observed in the primary analysis translates to an OS advantage at 5 years in the first-line setting

*HRD defined as a BRCAm and/or genomic instability score ≥42.
BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; OS, overall survival; PFS, progression-free survival.

1. Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28.

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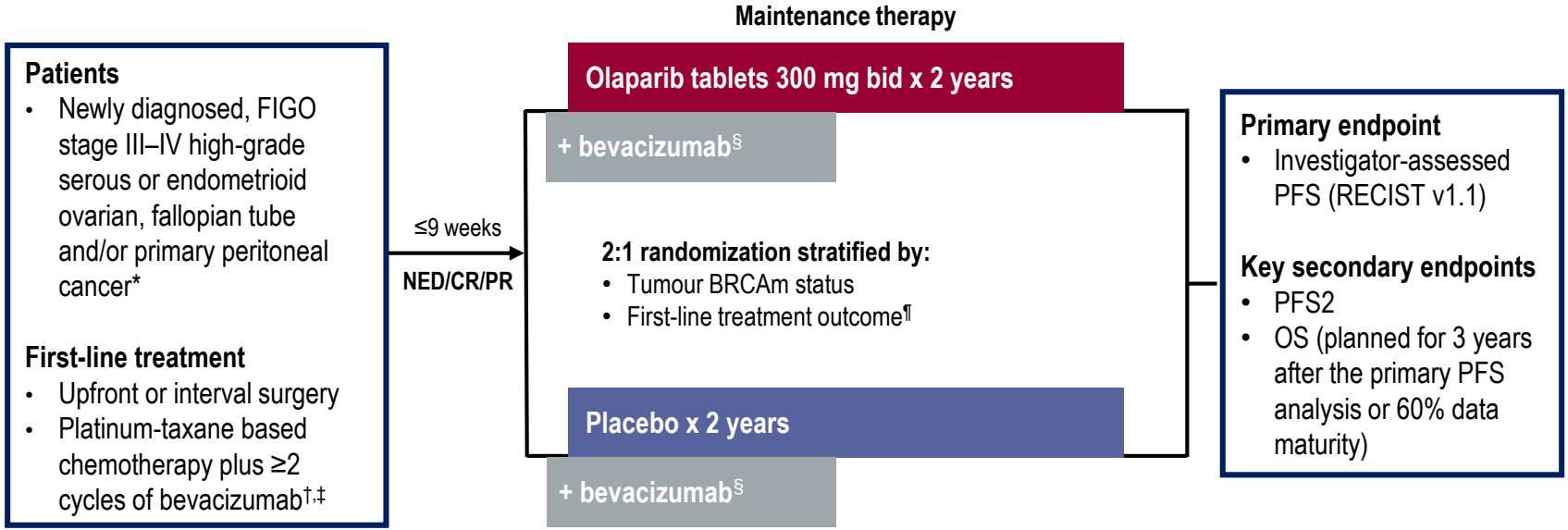
PAOLA-1 trial design



*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; †Patients must have received ≥4 and ≤9 cycles of platinum-based chemotherapy; ‡Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, 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; ¶According to timing of surgery and NED/CR/PR.
bid, twice daily; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline BRCA mutation; NED, no evidence of disease; PBC, platinum-based chemotherapy; PFS2, time from randomization to second progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

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Statistical analysis

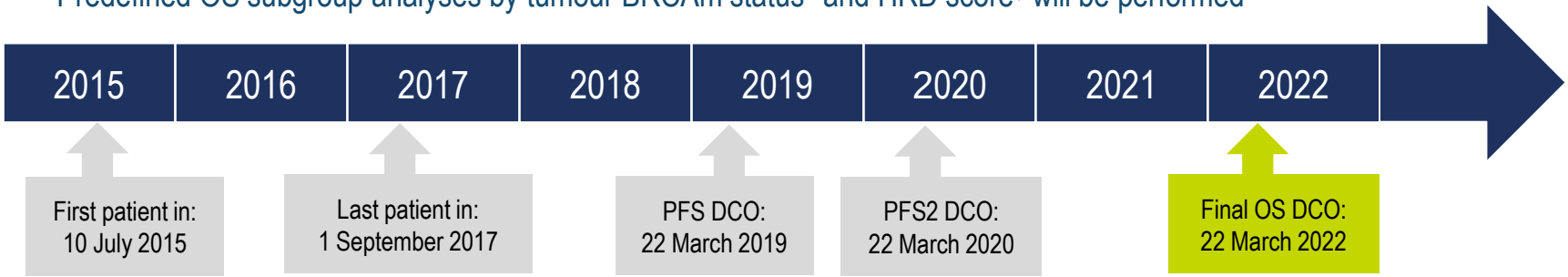
- A hierarchical testing strategy was applied for key endpoints

PFS — Statistically significant **PFS achieved**

PFS2 — Statistically significant **PFS2 achieved**

OS — **OS** will be tested at full 5% alpha at final OS DCO

- Predefined OS subgroup analyses by tumour BRCAm status* and HRD score† will be performed



*By central labs; †By Myriad myChoice HRD Plus; defined as genomic instability score ≥42.
DCO, data cutoff.

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Patient characteristics

		Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Age, median, years (range)		61 (32–87)	60 (26–85)
FIGO stage, n (%)	III	378 (70)	186 (69)
	IV	159 (30)	83 (31)
HRD status,* n (%)	HRD positive	255 (47)	132 (49)
	tBRCAm	157 (29)	80 (30)
	HRD positive excluding tBRCAm	97 (18)	55 (20)
	HRD negative/HRD unknown	282 (53)	137 (51)
	HRD negative	192 (36)	85 (32)
History of cytoreductive surgery, n (%)	Upfront surgery	271 (50)	138 (51)
	• No residual macroscopic disease	160 (59)	85 (62)
	• Residual macroscopic disease	111 (41)	53 (38)
	Interval cytoreductive surgery	228 (42)	110 (41)
	• No residual macroscopic disease	163 (71)	75 (68)
	• Residual macroscopic disease	65 (29)	35 (32)
	No surgery	38 (7)	21 (8)
Response after surgery/PBC, n (%)	NED	290 (54)	141 (52)
	CR	106 (20)	53 (20)
	PR	141 (26)	75 (28)

*BRCAm status by central labs and HRD status by Myriad myChoice HRD Plus; patients in tBRCAm and HRD positive excluding tBRCAm subgroups do not equal the total number of patients in the HRD-positive subgroup because of different testing methods.
tBRCAm, tumour BRCAm.

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tBRCAm, tumour BRCAm.

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Patient disposition at final DCO

		Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Randomized, n		537	269
Treated, n (%)		535	267
Patients who withdrew from study, n (%)	Total	537 (100)	269 (100)
	Patient lost to follow-up	6 (1)	0 (0)
	Death	286 (53)	158 (59)
	Consent withdrawn	15 (3)	6 (2)
	Study completed	230 (43)	105 (39)
Median duration of treatment,* months	Olaparib/placebo	17.3	15.6
	Bevacizumab	11.0	10.6
Median duration of follow-up for OS, months (IQR)		61.7 (57.5–67.0)	61.9 (58.1–66.8)

*Median duration of treatment with bevacizumab since randomization.
IQR, interquartile range.

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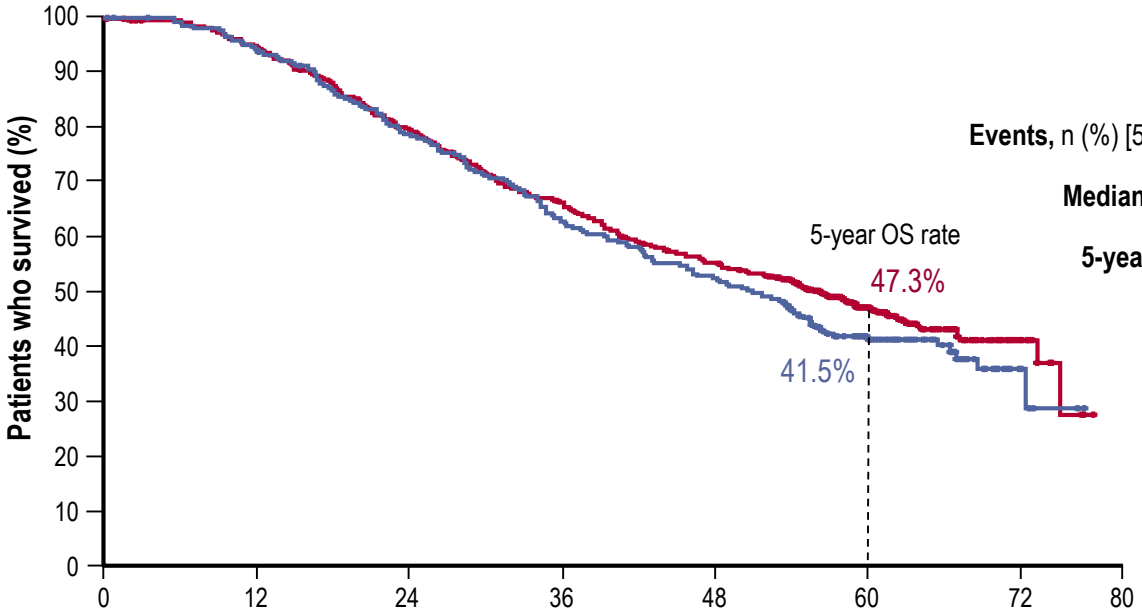
OS analysis: ITT population



No. at risk																									
Olaparib + bevacizumab	537	530	528	517	503	480	463	440	420	398	376	357	347	329	308	295	286	276	262	217	169	113	82	40	19	4	0
Placebo + bevacizumab	269	267	264	261	250	242	229	220	208	199	188	179	166	160	154	146	139	132	121	96	76	51	37	20	5	2	0

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [55% maturity]	288 (53.6)	158 (58.7)
Median OS, months	**56.5**	**51.6**
5-year OS rate, %	**47.3**	**41.5**

HR 0.92 (95% CI 0.76–1.12);
***P*=0.4118**

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **19.6%** (105/537)
Placebo + bevacizumab: **45.7%** (123/269)

Median time from first cycle of chemotherapy to randomization = 6 months

PARP, poly(ADP-ribose) polymerase.

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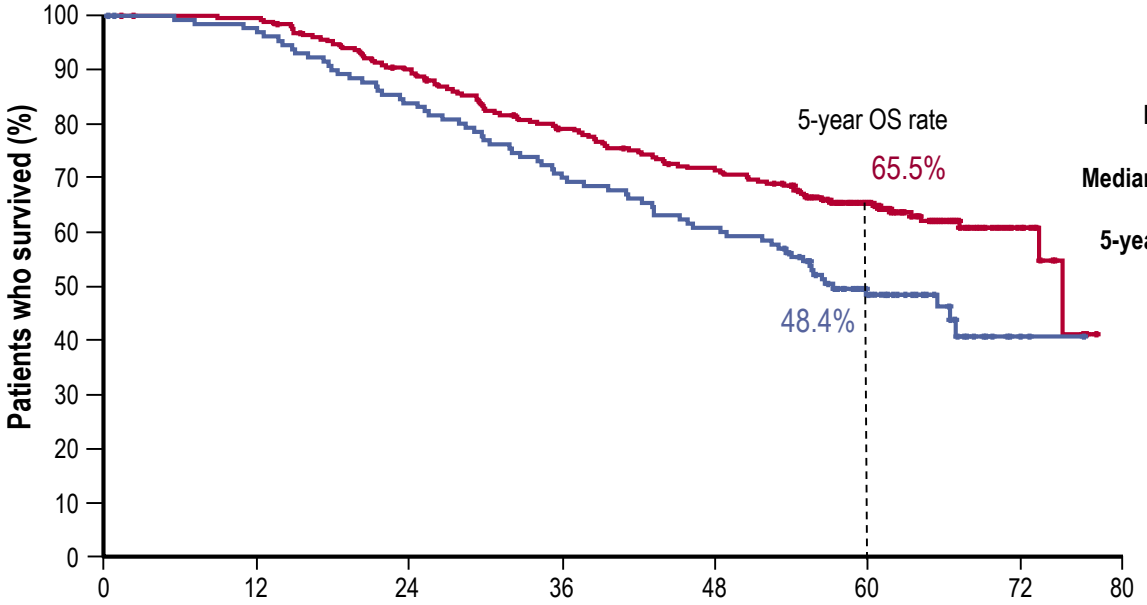
OS was prolonged in the HRD-positive subgroup



No. at risk																									
Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62 (95% CI 0.45–0.85)

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

*Median unstable; <50% data maturity.
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

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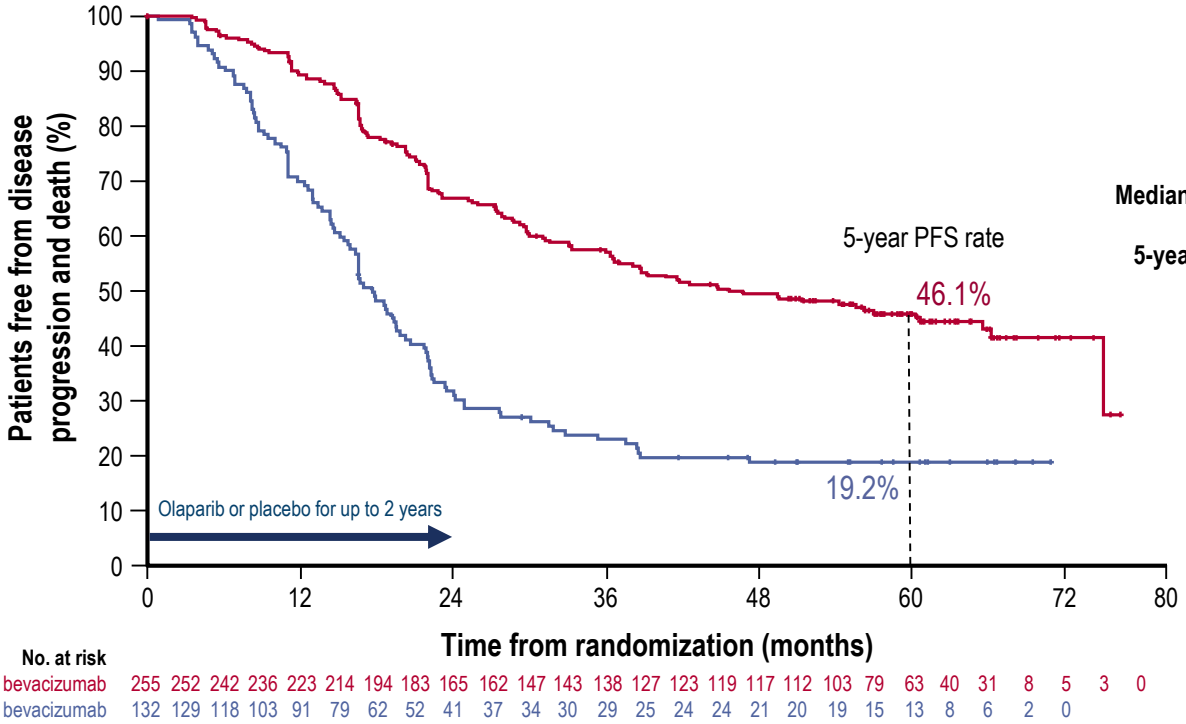
Updated PFS: HRD-positive population*



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	136 (53.3)	104 (78.8)
Median PFS, months	**46.8**	**17.6**
5-year PFS rate, %	**46.1**	**19.2**

HR 0.41 (95% CI 0.32–0.54)

59% reduction in risk of disease progression or death for olaparib + bevacizumab vs bevacizumab alone

*Descriptive analysis; PFS by investigator-assessment (modified RECIST v1.1).

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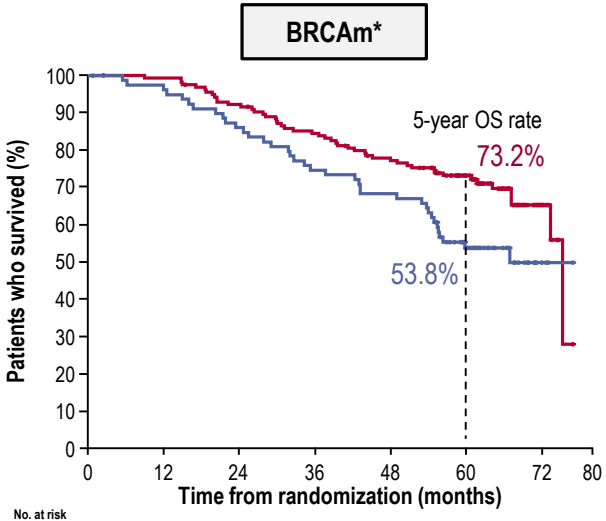
OS subgroup analysis by BRCAm and HRD status

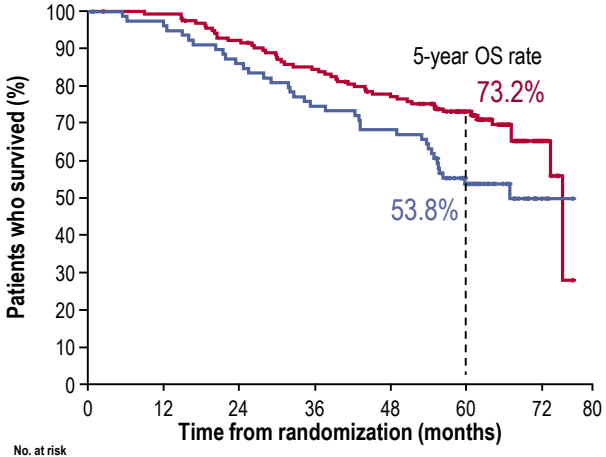


	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

OS subgroup analysis by BRCAm and HRD status

BRCAm*



No. at risk

Olaparib + bevacizumab	157	156	156	155	155	152	150	144	143	139	134	131	130	127	123	118	117	115	112	99	80	55	42	21	11	2	0
Placebo + bevacizumab	80	79	78	77	76	74	72	71	68	66	64	61	59	58	58	54	54	53	50	40	33	22	17	10	3	1	0

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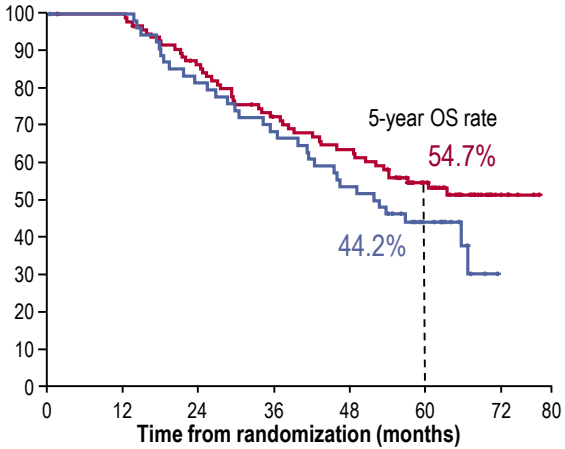
	HR 0.60 (95% CI 0.39–0.93)	

HRD positive‡ excluding BRCAm



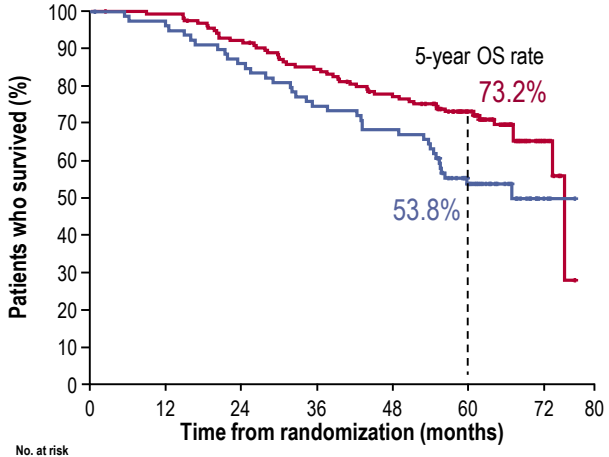
	97	96	96	96	96	91	87	86	81	76	71	70	66	63	61	59	58	55	52	45	37	29	22	12	5	2	0
	55	54	54	54	54	51	48	46	44	42	40	39	37	36	33	32	29	28	24	21	15	9	6	2	0		

Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
44 (45.4)	32 (58.2)
NR	52.0
54.7	**44.2**
9 (9.3)	23 (41.8)
HR 0.71 (95% CI 0.45–1.13)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

OS subgroup analysis by BRCAm and HRD status

BRCAm*



No. at risk

Olaparib + bevacizumab	157	156	156	155	155	152	150	144	143	139	134	131	130	127	123	118	117	115	112	99	80	55	42	21	11	2	0
Placebo + bevacizumab	80	79	78	77	76	74	72	71	68	66	64	61	59	58	58	54	54	53	50	40	33	22	17	10	3	1	0

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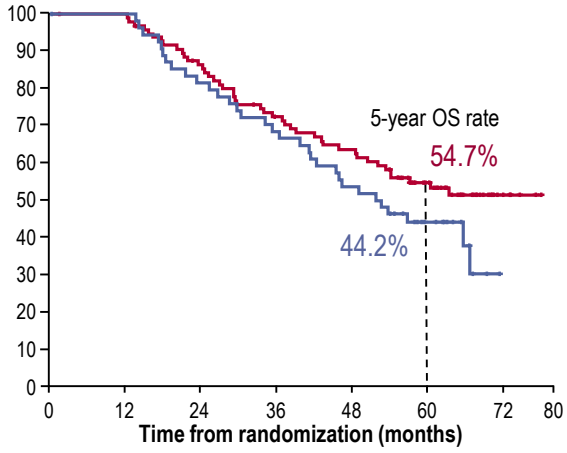
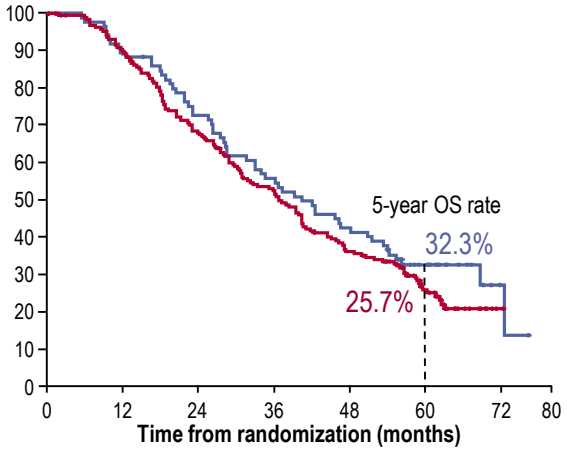
HRD positive‡ excluding BRCAm



	97	96	96	96	96	91	87	86	81	76	71	70	66	63	61	59	58	55	52	45	37	29	22	12	5	2	0
	55	54	54	54	54	51	48	46	44	42	40	39	37	36	33	32	29	28	24	21	15	9	6	2	0		

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	44 (45.4)	32 (58.2)
	NR	52.0
	54.7	**44.2**
	9 (9.3)	23 (41.8)
HR 0.71 (95% CI 0.45–1.13)		

HRD negative†



	192	187	186	179	169	157	146	135	126	119	109	100	97	89	77	72	66	62	57	43	30	16	11	5	1	0	
	85	85	84	83	76	74	71	65	60	56	51	48	46	43	41	38	35	33	31	21	17	11	8	5	2	1	0

	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
	140 (72.9)	58 (68.2)
	36.8	40.4
	25.7	**32.3**
	46 (24.0)	34 (40.0)
HR 1.19 (95% CI 0.88–1.63)		

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

AEs of special interest

	Primary PFS analysis (DCO: 22 March 2019)		Final PFS2 analysis (DCO: 22 March 2020)	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	7 (1.3)	4 (1.5)
New primary malignancies, n (%)	7 (1.3)	3 (1.1)	13 (2.4)	5 (1.9)
Pneumonitis/ILD/bronchiolitis, n (%)	6 (1.1)	0 (0.0)	6 (1.1)	0 (0.0)

- All patients had discontinued treatment at PFS2 DCO
- TEAEs have been reported previously[1,2] and the olaparib safety profile has been well characterized

AA, aplastic anaemia; AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome.

1. Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28; 2. González-Martín A *et al. Eur J Cancer* 2022;174:221–31.

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AEs of special interest

	Primary PFS analysis (DCO: 22 March 2019)		Final PFS2 analysis (DCO: 22 March 2020)		Final OS analysis (DCO: 22 March 2022)	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	7 (1.3)	4 (1.5)	9 (1.7)	6 (2.2)
New primary malignancies, n (%)*	7 (1.3)	3 (1.1)	13 (2.4)	5 (1.9)	22 (4.1)	8 (3.0)
Pneumonitis/ILD/bronchiolitis, n (%)†	6 (1.1)	0 (0.0)	6 (1.1)	0 (0.0)	7 (1.3)	2 (0.7)

- All patients had discontinued treatment at PFS2 DCO
- TEAEs have been reported previously[1,2] and the olaparib safety profile has been well characterized

*New primary malignancies were: 1 plasma cell myeloma, 2 basal cell carcinoma, 11 breast cancer, 1 bronchial carcinoma, 1 colon cancer, 1 glioblastoma, 1 malignant neoplasm, 1 pancreatic carcinoma, 2 squamous cell carcinoma, and 1 ureteric cancer in the olaparib arm; and 1 papillary thyroid cancer, 4 breast cancer, 1 diffuse large B-cell lymphoma, 1 malignant lung neoplasm, and 1 malignant neoplasm in the placebo arm;
†Pneumonitis/ILD/bronchiolitis events were: 1 bronchiolitis, 1 pneumonia, 1 acute respiratory distress syndrome, 2 interstitial lung disease, and 2 pneumonitis in the olaparib arm; and 1 corona virus infection and 1 pneumonitis case in the placebo arm.

AA, aplastic anaemia; AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome.

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Conclusions

- In the PAOLA-1/ENGOT-ov25 trial, despite 50% of patients in the control arm receiving a PARP inhibitor post-progression, the addition of maintenance olaparib to bevacizumab provided a clinically meaningful OS benefit in patients who were HRD positive (5-year OS rate: 65.5% vs 48.4%; HR 0.62, 95% CI 0.45–0.85)
  - A clinically meaningful benefit was observed in HRD-positive patients regardless of BRCAm status
- No OS difference was observed in the HRD-negative subgroup
- No new safety signals were observed with longer-term follow-up
  - Incidence of MDS/AML and new primary malignancies remained low and balanced between arms
- These data confirm the addition of olaparib to bevacizumab as a standard of care for HRD-positive patients in this setting, and the importance of precision medicine and biomarker testing to guide treatment decisions

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A Abecassis, S Armanet, S Brutto, D Cardoso, A Lasfargues, C Montoto-Grillot, B Votan

Study group coordinators
AGO De: G Elser, N Cron
AGO Au: R Berger, A Riha
BGOG: E Peeraer
MITO and **MANGO:** P Gargiulo
GEICO: A Levin
GOTIC: H Shinyama
NSGO: K Pors

IDMC
J Vermorken
S Kaye
G Pond

Ascopharm Gr Novasco
P Aubert

Statisticians
D Perol
S Chabaud
C Cropet
QOL: A Anota

Screening platforms
Institut Curie
Gustave Roussy
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