XXII ASSEMBLEA MaNGO MILANO

STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-29th, 2025

Responsabili Scientifici:
NICOLETTA COLOMBO, FRANCESCO RASPAGLIESI

MaNGO

Tailoring the treatment in ovarian cancer
The updated maintenance treatment algorithm

Nicoletta Colombo

Disclosures

- **Employee**: University of Milan-Bicocca and European Institute of Oncology IRCCS, Milan
- **Consultant/Advisor**: AstraZeneca, Clovis Oncology, Eisai, GSK, Immunogen, Mersana, MSD/Merck, Nuvation Bio, Oncxerna, Pieris, Roche, Novocure
- **Promotional Speaker**: AstraZeneca, Clovis, MSD/Merk, GlaxoSmithKline, Eisai
- **Investigator/Researcher**: AstraZeneca, GSK, Roche
- **Nonfinancial interests**: Steering Committee Member for ESMO Clinical Guidelines, Chair Scientific Committee ACTO onlus

ESMO guidelines

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

A. González-Martin[1], P. Harter[2], A. Leary[3], D. Lorusso[4,5], R. E. Miller[6,7], B. Pothuri[8], I. Ray-Coquard[9], D. S. P. Tan[10,11,12,13], E. Bellet[14], A. Oaknin[15] & J. A. Ledermann[16], on behalf of the ESMO Guidelines Committee*

6 cycles of carboplatin+paclitaxel +/- Bevacizumab remain the SOC

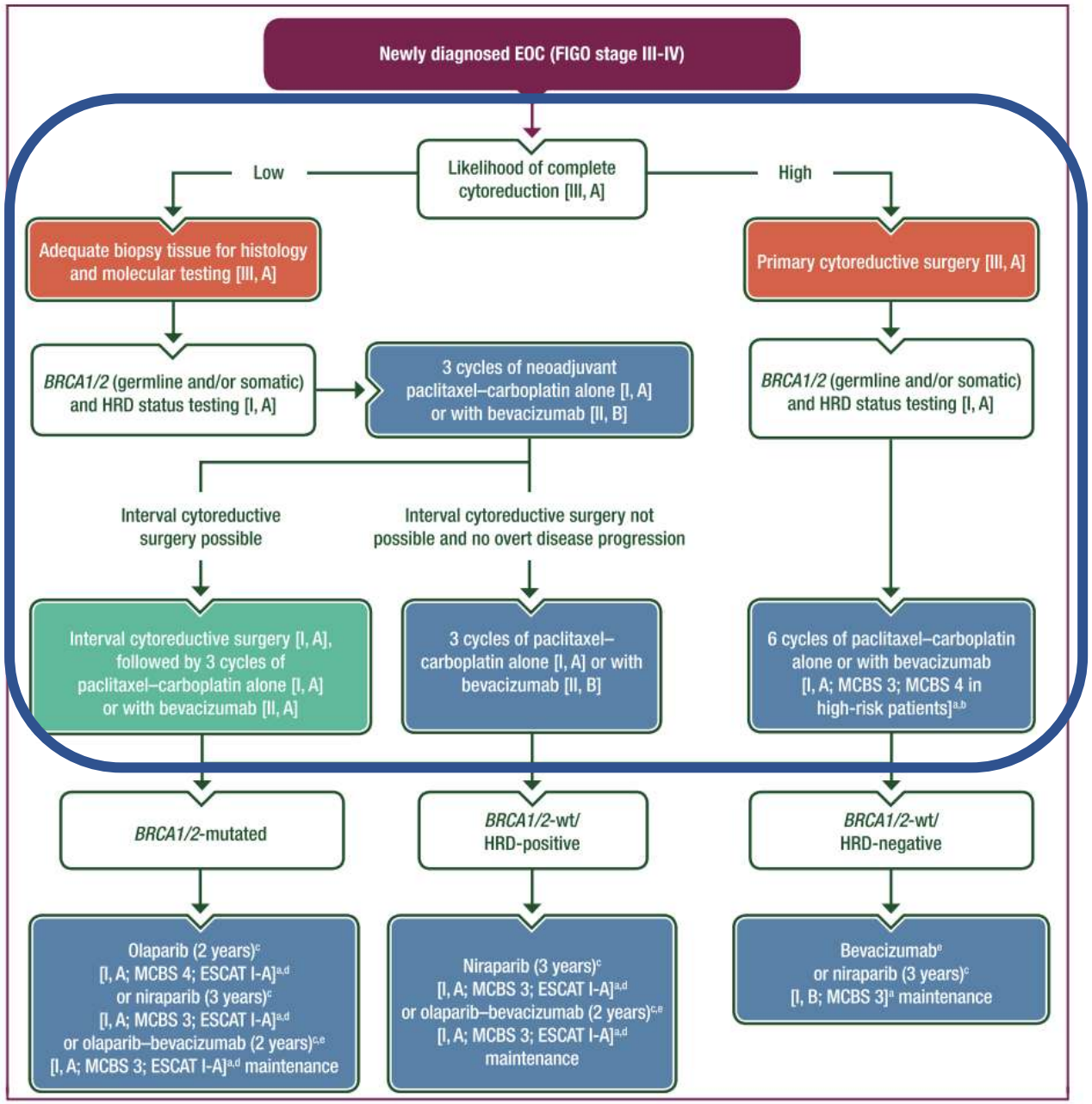
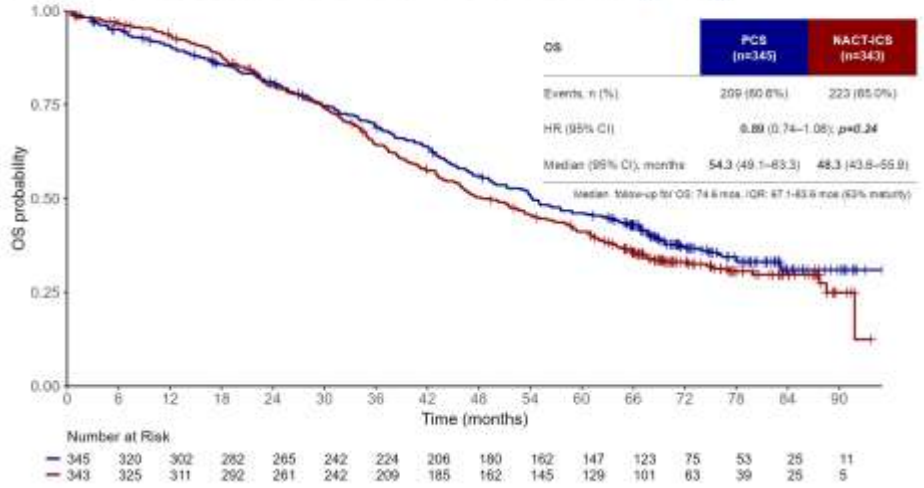


Figure 2. Management of advanced EOC (FIGO stage III-IV).

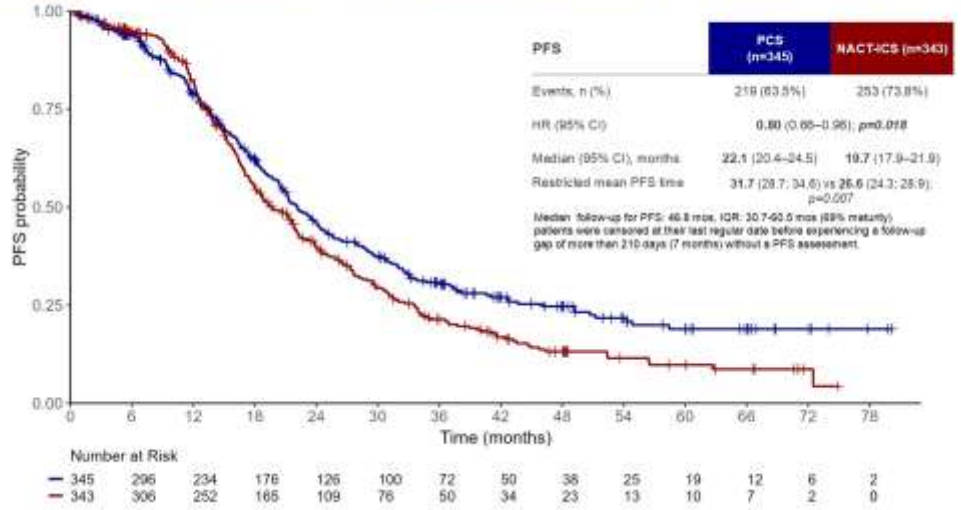
Gonzalez-Martin, Ann Oncol 2023

Primary debulking surgery still matters!!!

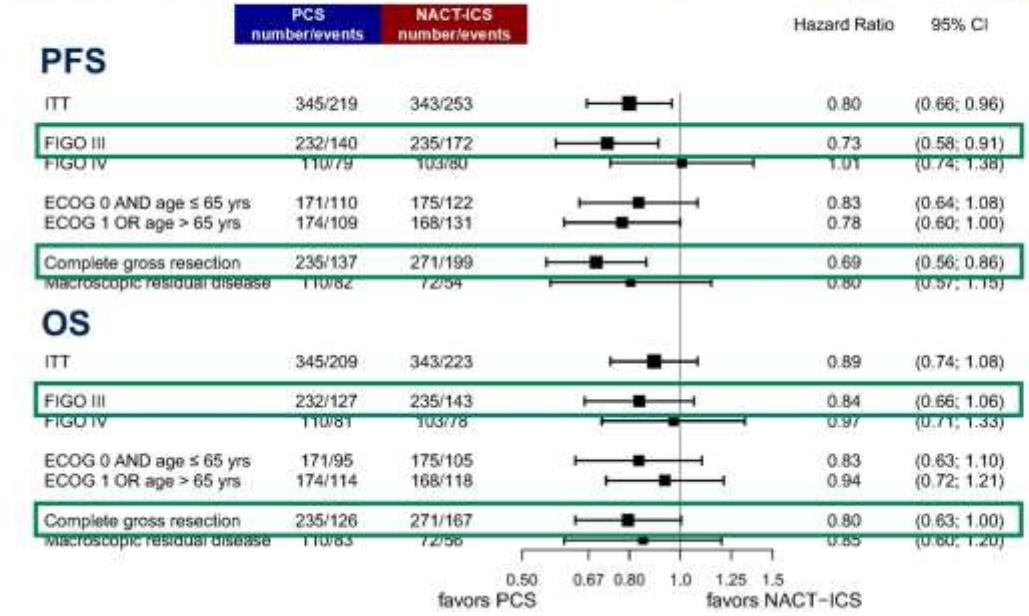
TRUST Results: Overall Survival (ITT)



TRUST Results: Progression-free Survival (ITT)

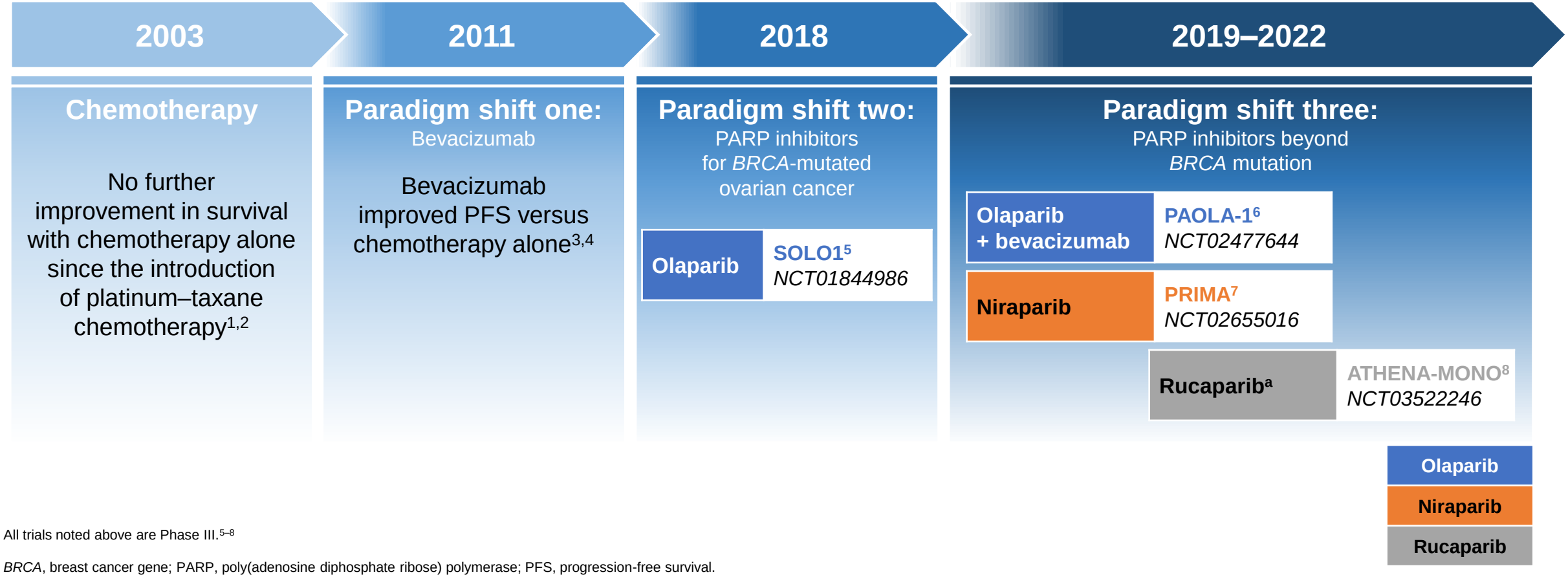


TRUST Results: Treatment Effects According to Subgroups



Sven Mahner, ASCO 2025

Significant progress has been made in the first-line management of ovarian cancer



All trials noted above are Phase III.[5–8]

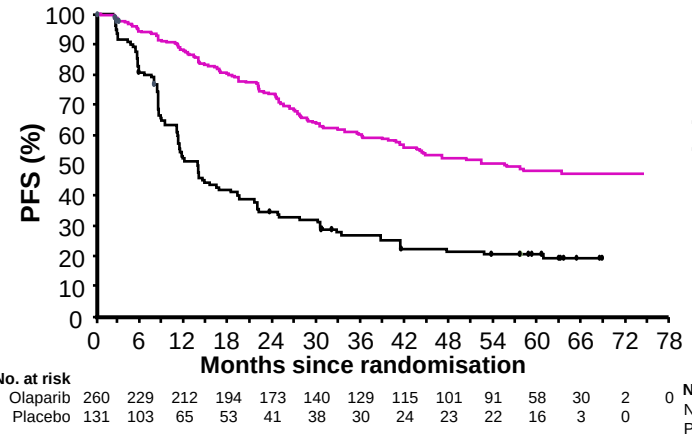
BRCA, breast cancer gene; PARP, poly(adenosine diphosphate ribose) polymerase; PFS, progression-free survival.

1. McGuire WP, et al. *N Engl J Med* 1996;334:1–6; 2. du Bois A, et al. *J Natl Cancer Inst* 2003;95:1320–1329; 3. Burger RA, et al. *N Engl J Med* 2011;365:2473–2483; 4. Perren TJ, et al. *N Engl J Med* 2011;365:2484–2496; 5. ClinicalTrials.gov. NCT01844986. Available at: https://clinicaltrials.gov/ct2/show/NCT01844986 (accessed February 2024); 6. ClinicalTrials.gov. NCT02477644. Available at: https://clinicaltrials.gov/ct2/show/NCT02477644 (accessed February 2024); 7. ClinicalTrials.gov. NCT02655016. Available at: https://clinicaltrials.gov/ct2/show/NCT02655016 (accessed February 2024); 8. Monk JM, et al. *J Clin Oncol* 2022;40:3952–3964.

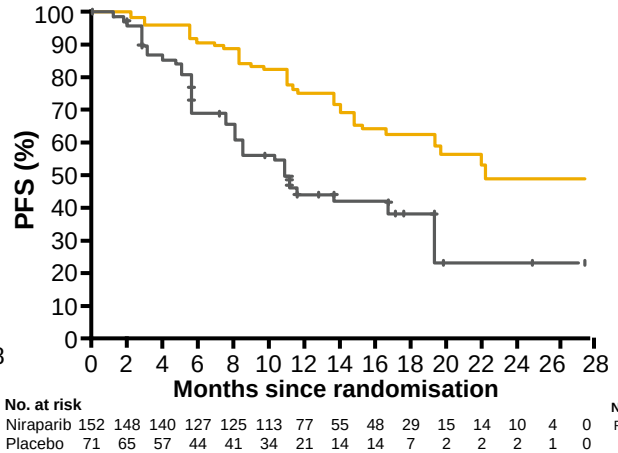
Significant extension in PFS in frontline PARP inhibitor maintenance trials in *BRCA*m ovarian cancer

PARPi monotherapy *versus* watch and wait

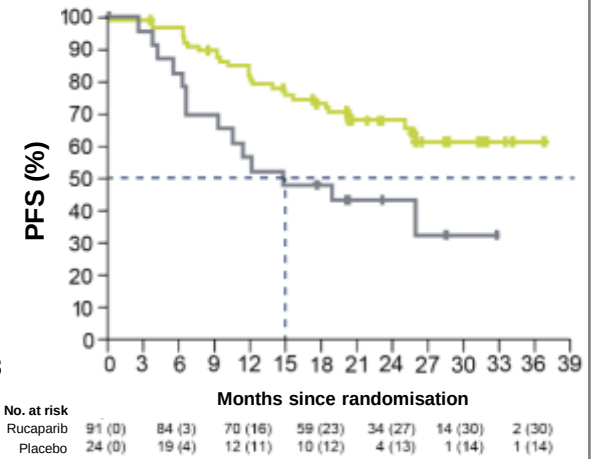
SOLO1[1]



PRIMA[2,3]



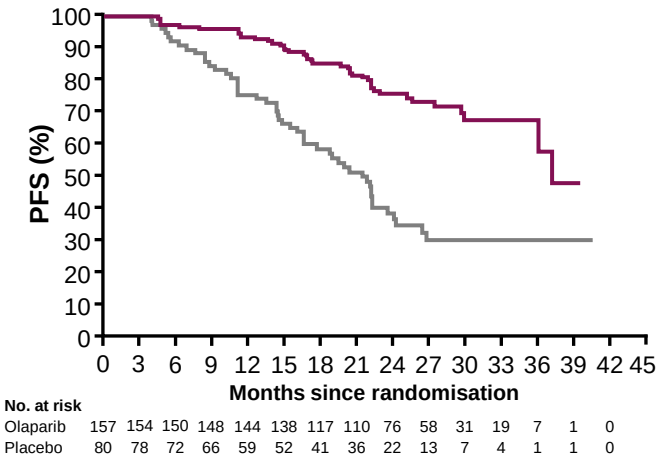
ATHENA-MONO[4]



	Olaparib (n=260)	Placebo (n=131)	Niraparib (n=152)	Placebo (n=71)	Rucaparib (n=91)	Placebo (n=24)
Events, n (%)	118 (45)	100 (76)	49 (32.2)	40 (56.3)		
Median PFS, months	**56.0**	**13.8**	**22.1**	**10.9**	**NR**	**14.7**
Δ Median PFS	**42.2 months**		**11.2 months**		**N/A**	
HR (95% CI)	0.33 (0.25-0.43)		0.40 (0.27-0.62),		0.40 (0.21-0.75),	

Olaparib plus bev combination *versus* bev maintenance

PAOLA-1[5]



	Olaparib + Bev (n=157)	Placebo + Bev (n=80)
Events, n (%)	41 (26)	49 (61)
Median PFS, months	**37.2**	**21.7**
Δ Median PFS	**15.5 months**	
HR (95% CI)	0.31 (0.20-0.47),	

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended

Bev, bevacizumab; *BRCA*, breast cancer susceptibility gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; HR, hazard ratio; N/A, not available; NR, not reached; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

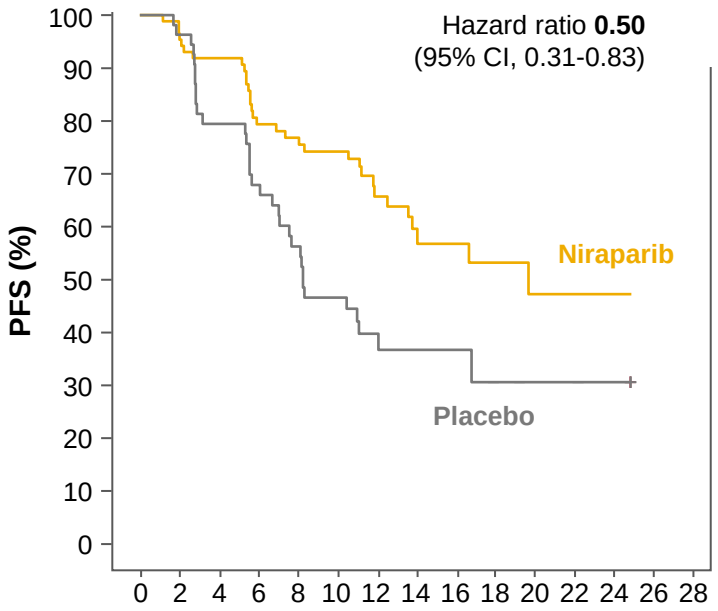
1. Bradley W, et al. Presented at: SGO 2021. Abstract 10520; 2. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402; 3. González-Martín A, et al. Presented at: ESMO 2019. Presentation 4627; 4. Monk BJ, et al. *J Clin Oncol.* 2022;40(34):3952-3964; 5. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2416-2428

Exploratory analysis of PFS with PARPi maintenance in patients with *BRCA*wt HRD-positive (high GIS) ovarian cancer

PARPi monotherapy *versus* watch and wait

PRIMA[1]

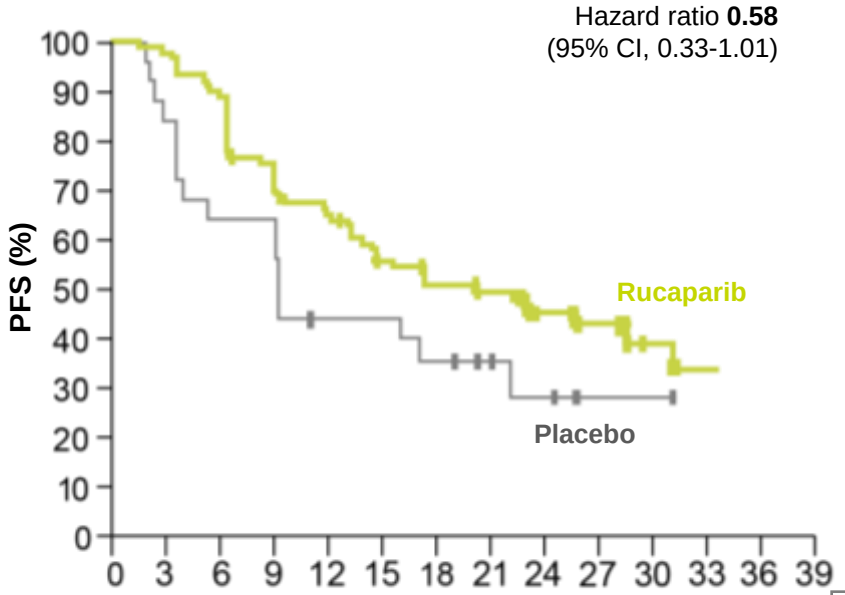
Myriad MyChoice®: HRD positive



No. at risk													
Niraparib	95	83	75	62	59	55	34	21	18	13	7	5	3
Placebo	55	52	42	35	29	23	13	7	7	4	3	3	2

ATHENA-MONO[2]

FoundationOne® CDx: High LOH

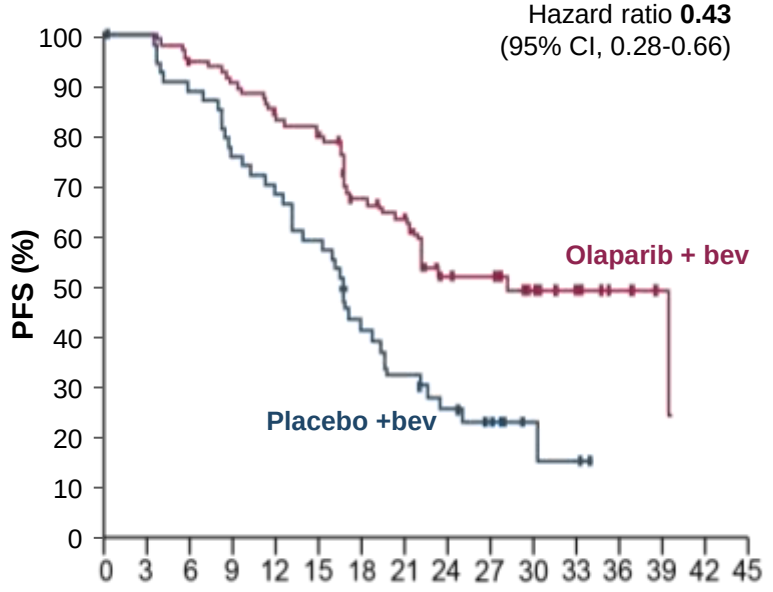


No. at risk							
Rucaparib	94 (0)	81 (9)	57 (30)	41 (43)	25 (47)	8 (49)	4 (50)
Placebo	25 (0)	16 (9)	10 (14)	8 (16)	4 (17)	1 (17)	0 (17)

Olaparib plus bev combination *versus* bev maintenance

PAOLA-1[3]

Myriad MyChoice®: HRD positive



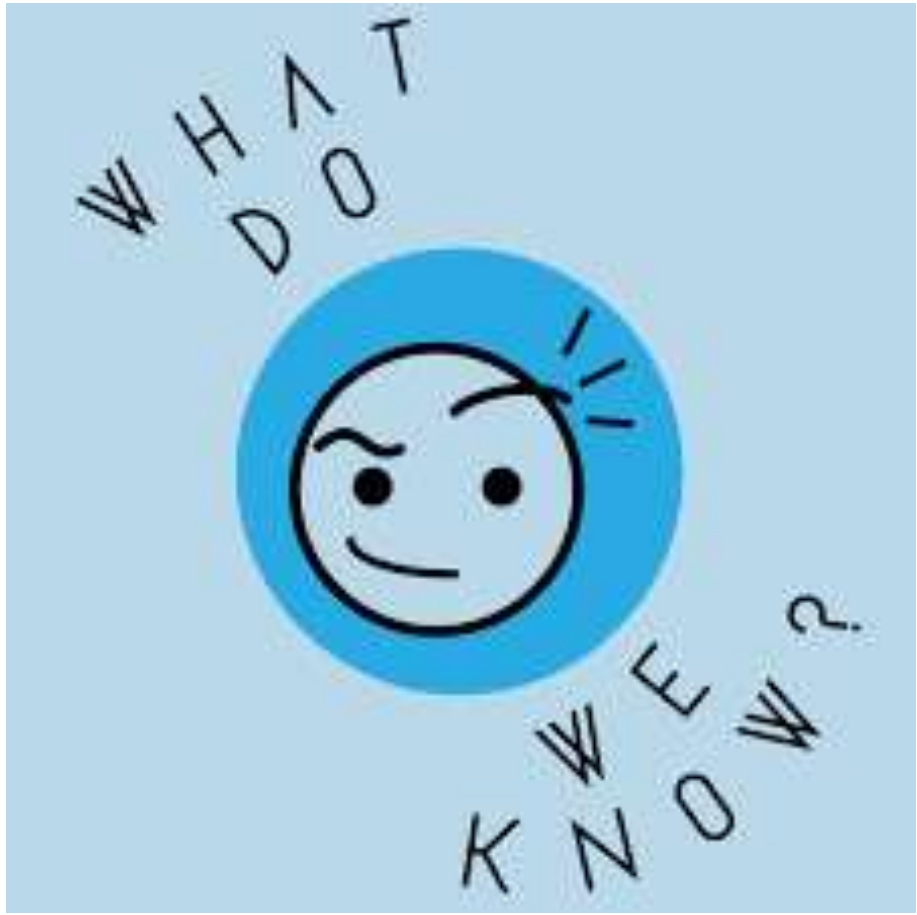
No. At Risk													
Olaparib	97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
Placebo	55	54	48	41	37	32	19	15	11	8	3	2	0		

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended

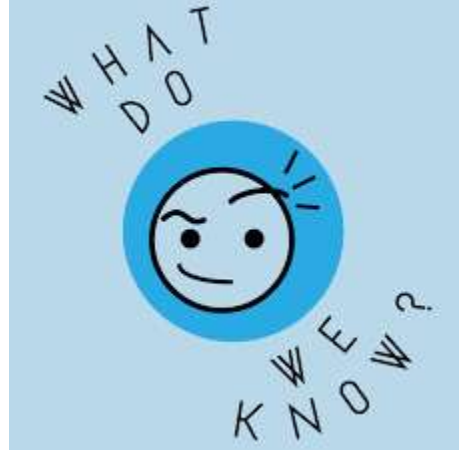
Bev, bevacizumab; *BRCA*, breast cancer susceptibility gene; *BRCA*wt, *BRCA* wild type; CDx, companion diagnostics; CI, confidence interval; GIS, genomic instability score; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor; PFS, progression-free survival.

1. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402; 2. Monk BJ, et al. Presented at: SGO 2020. Seminal abstract 31; 3. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2416-2428.

What do we know?



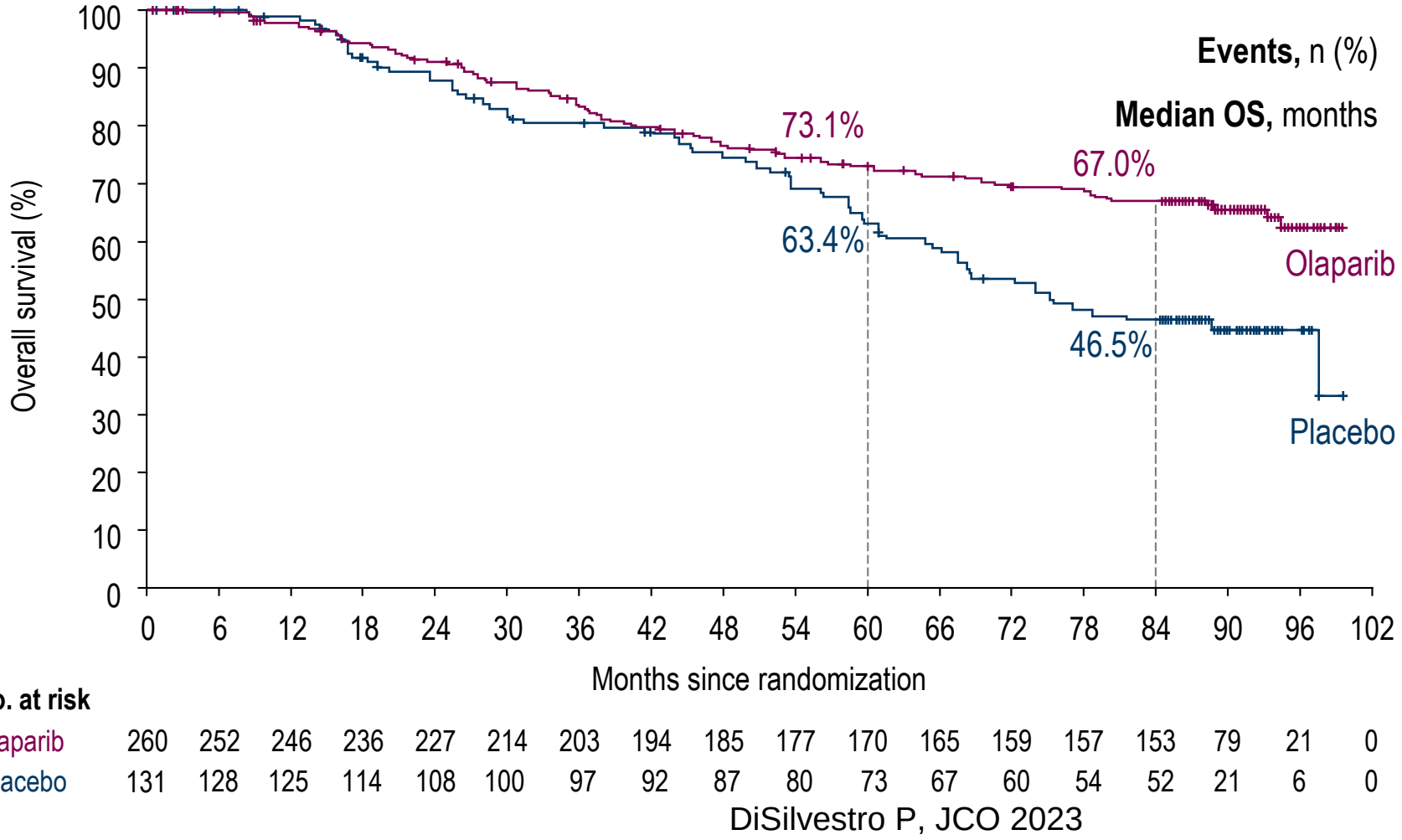
What do we know?



- All patients should be tested for BRCA and HRD
- All patients with BRCAm and/or HRD+ test must receive a parp inhibitor as maintenance after response to platinum-based chemotherapy

OS analysis

Maintenance olaparib provided a clinically meaningful OS benefit



DiSilvestro P, JCO 2023

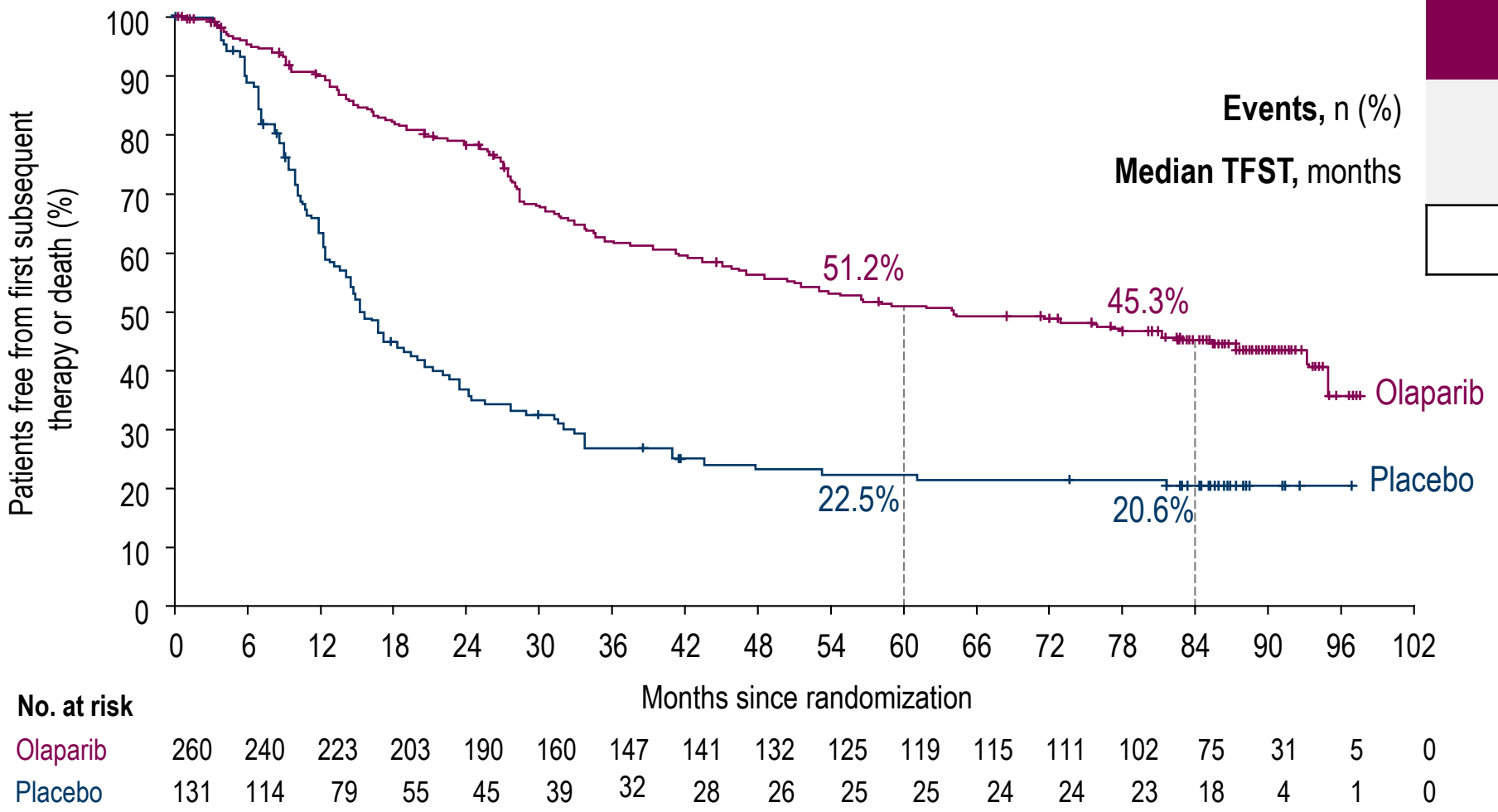
	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**

HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

**P*<0.0001 required to declare statistical significance

TFST substantially delayed by maintenance olaparib



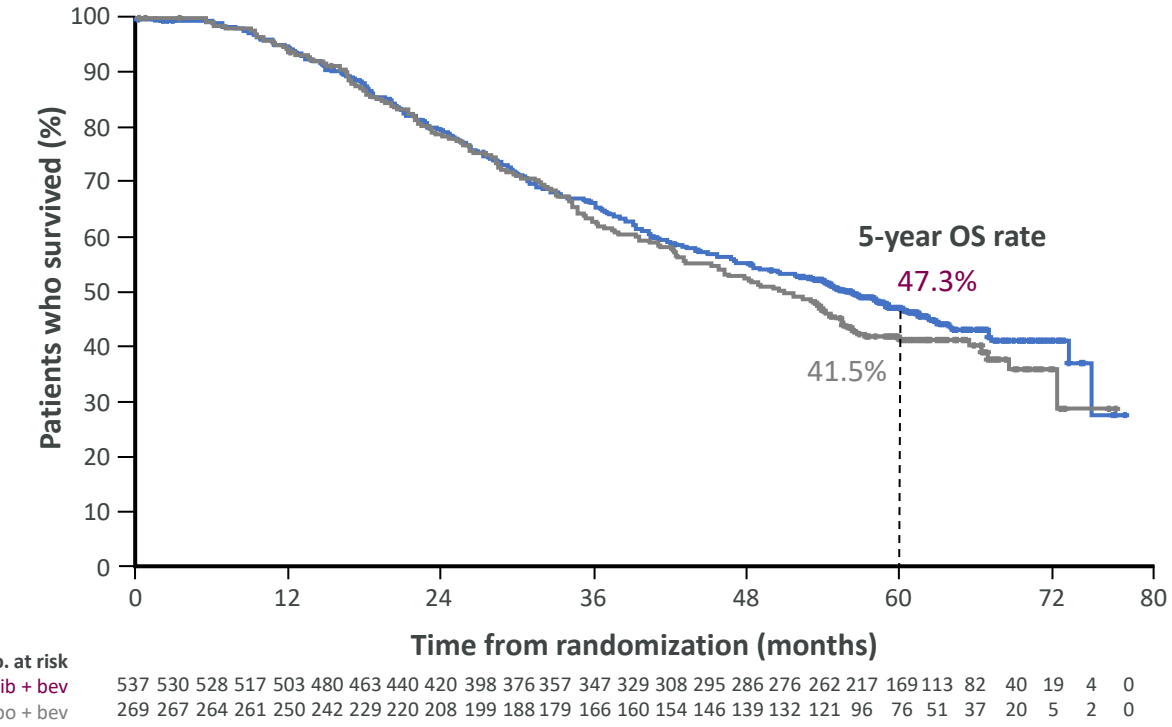
	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	**64.0**	**15.1**
HR 0.37 (95% CI 0.28–0.48)		

DiSilvestro P, JCO 2023

PAOLA 1: Final OS analysis

Data cut-off March 2022

Median OS was similar between both arms in the ITT population



	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

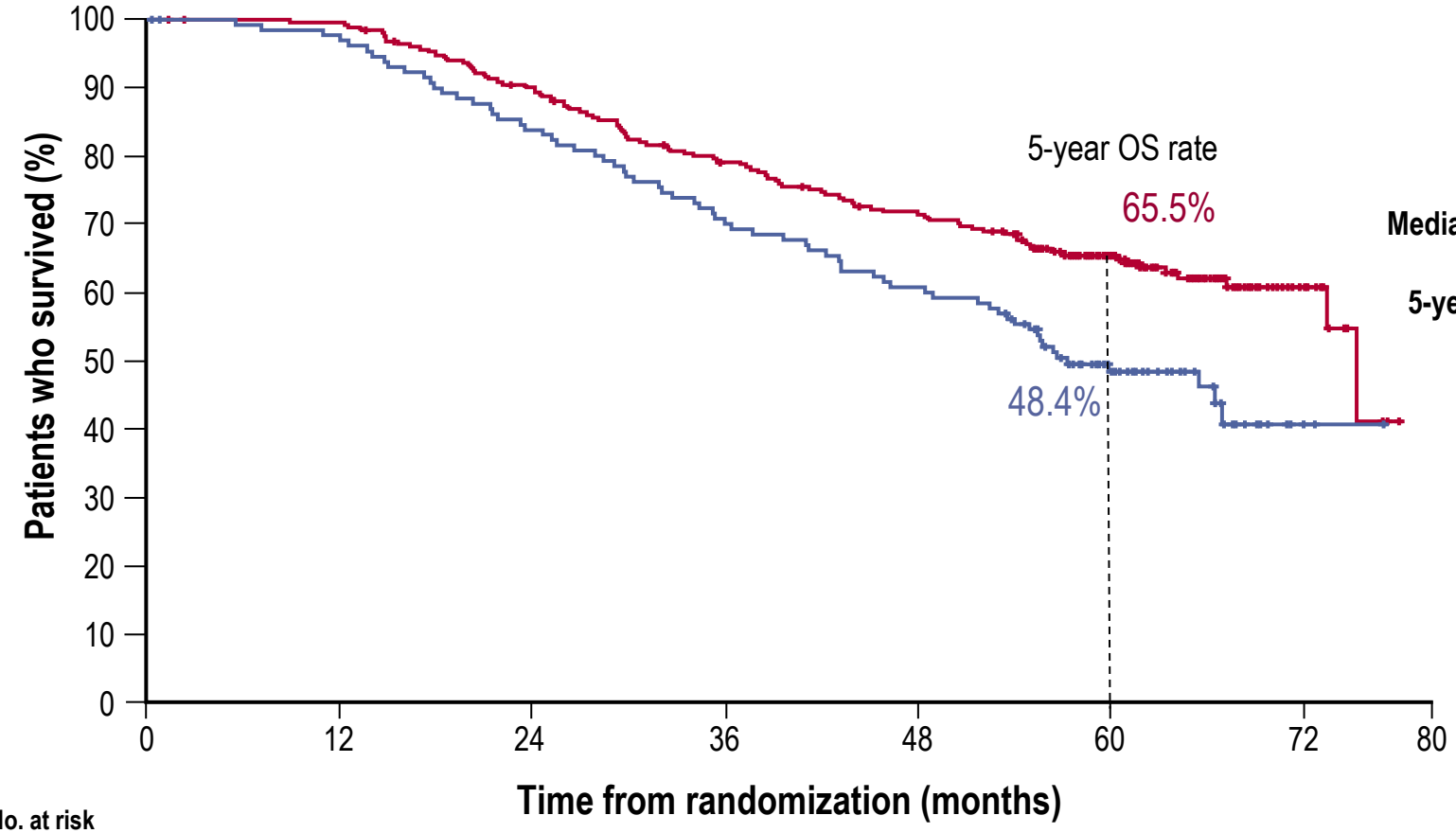
Patients receiving a PARP inhibitor during any subsequent treatment:
Olaparib + bev: **19.6%** (105/537)
Placebo + bev: **45.7%** (123/269)

Final OS DCO: 02 March 2022. Final OS analysis planned for 3 years after the primary PFS analysis or 60% data maturity.

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

Ray-Coquard I, Annals of Oncology Volume 34 Issue 8 Pages 681-692 (August 2023)

OS was prolonged in the HRD-positive subgroup



	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

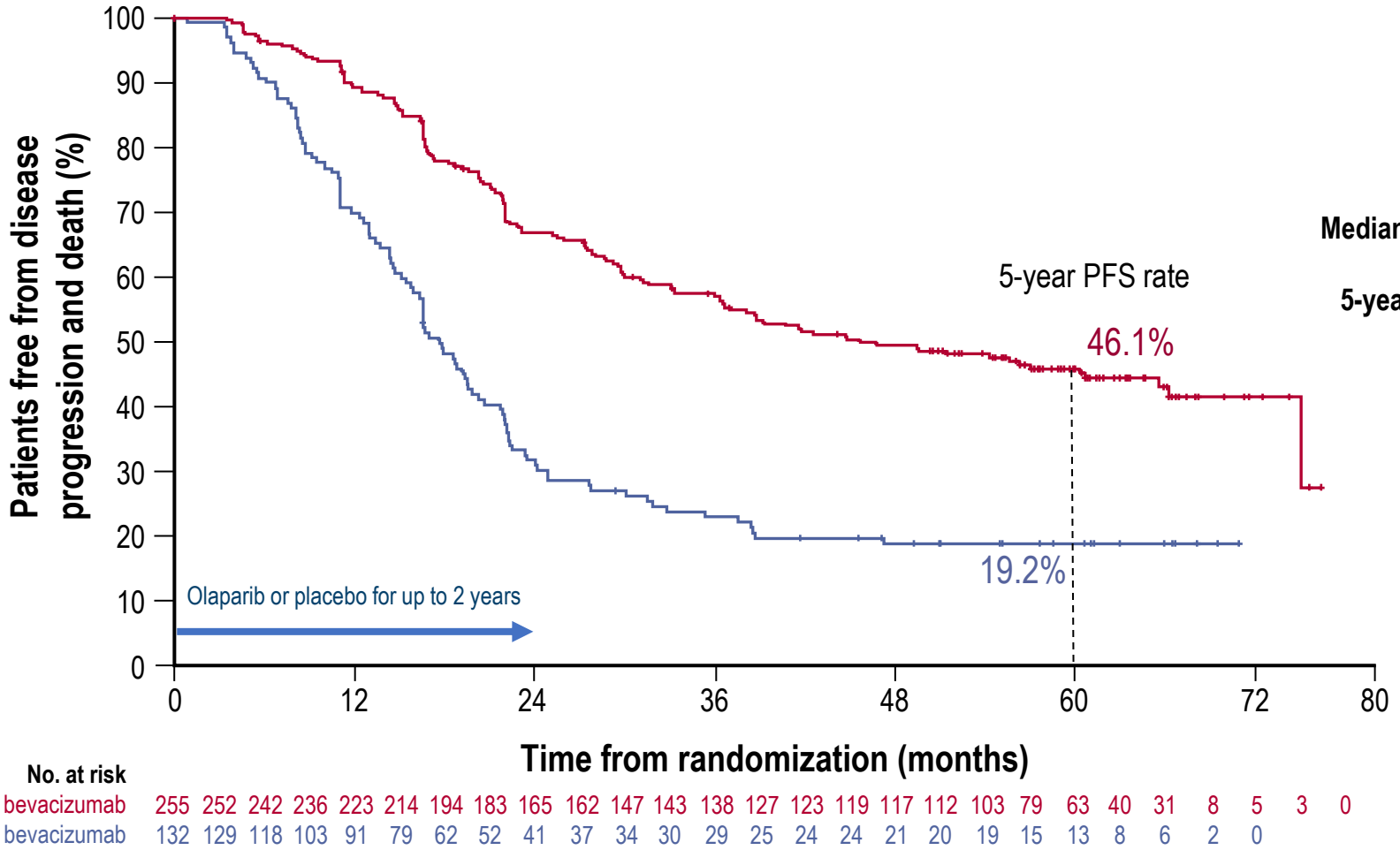
Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

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

*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.

Ray-Coquard I, Annals of Oncology Volume 34 Issue 8 Pages 681-692 (August 2023)

Updated PFS: HRD-positive population*



No. at risk																										
Olaparib + bevacizumab	255	252	242	236	223	214	194	183	165	162	147	143	138	127	123	119	117	112	103	79	63	40	31	8	5	3	0
Placebo + bevacizumab	132	129	118	103	91	79	62	52	41	37	34	30	29	25	24	24	21	20	19	15	13	8	6	2	0		

	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)

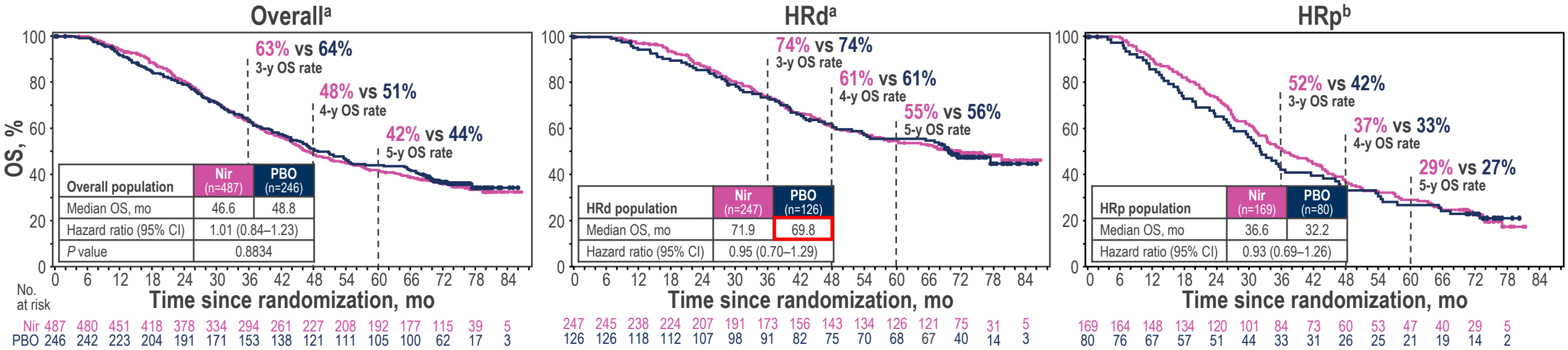
59% reduction in risk of disease progression or death for olaparib + bevacizumab vs bevacizumab alone

Ray-Coquard I, Annals of Oncology Volume 34 Issue 8 Pages 681-692 (August 2023)

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

PRIMA Final OS (62.5% maturity in overall population)

No difference in OS between niraparib and placebo arms in the overall, HRd, and HRp populations



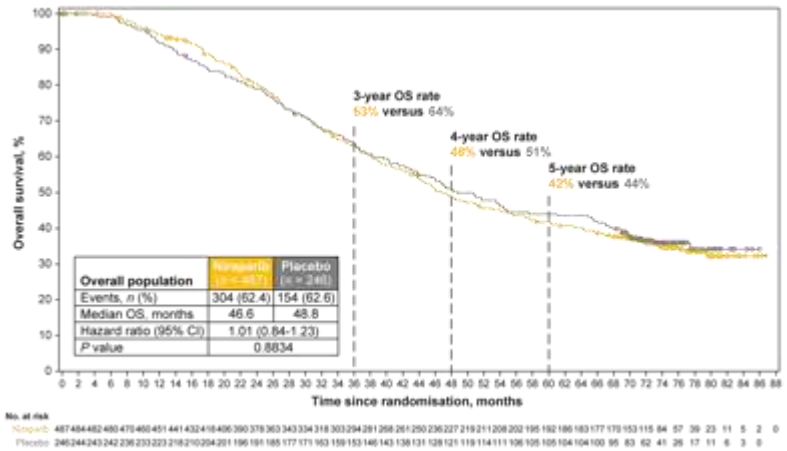
- OS results for all prespecified biomarker-defined subgroups consistent with overall population[c]
- Assessment of long-term efficacy outcomes in high-risk aOC may be complicated by multiple factors[1]
  - Patient population[2–4]
  - Extended postprogression survival[1,5]
  - Subsequent therapy[1,5]

[a]Hazard ratios and 95% CIs for overall and HRd populations calculated using stratified Cox proportional hazards model with randomization stratification factors. [b]Hazard ratio and 95% CI for HRp population calculated using unstratified Cox proportional hazards model. [c]OS results for the HRnd population (unstratified): hazard ratio (95% CI), 1.39 (0.88–2.19). aOC, advanced ovarian cancer; HRd, homologous recombination deficient; HRnd, homologous recombination status not determined; HRp, homologous recombination proficient; OS, overall survival; Nir, niraparib; PBO, placebo. 1. Matulonis UA, et al. *Cancer*. 2015;121(11):1737–1746. 2. Siegel RL, et al. *CA Cancer J Clin.* 2024;74(1):12–49. 3. Elattar A, et al. *Cochrane Database Syst Rev.* 2011;201(8):CD007565. 4. Sun C, et al. *PLoS One.* 2014;9(5):e95285. 5. Delgado A, et al. *Am J Cancer Res.* 2021;11(4):1121–1131.

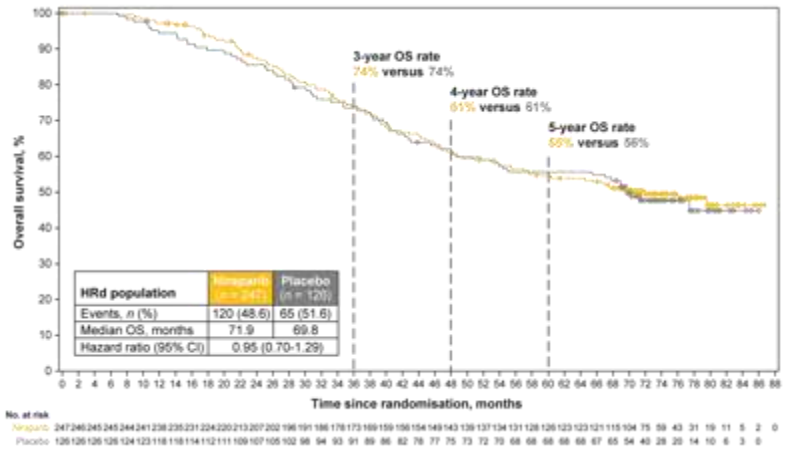
Antonio Gonzales, ESMO 2024; Monk B, et al. Ann Oncol.2024;35(11):981–992. ;

PRIMA : No difference in OS was seen between niraparib and placebo arms in the overall, HRd and HRp populations, BRCAm

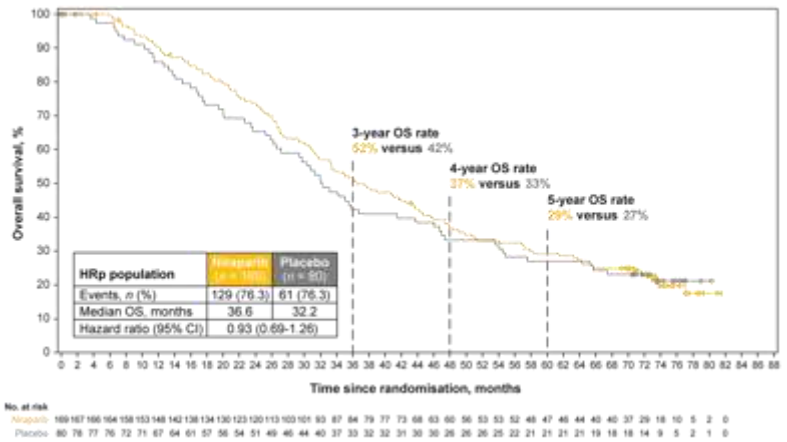
Overall



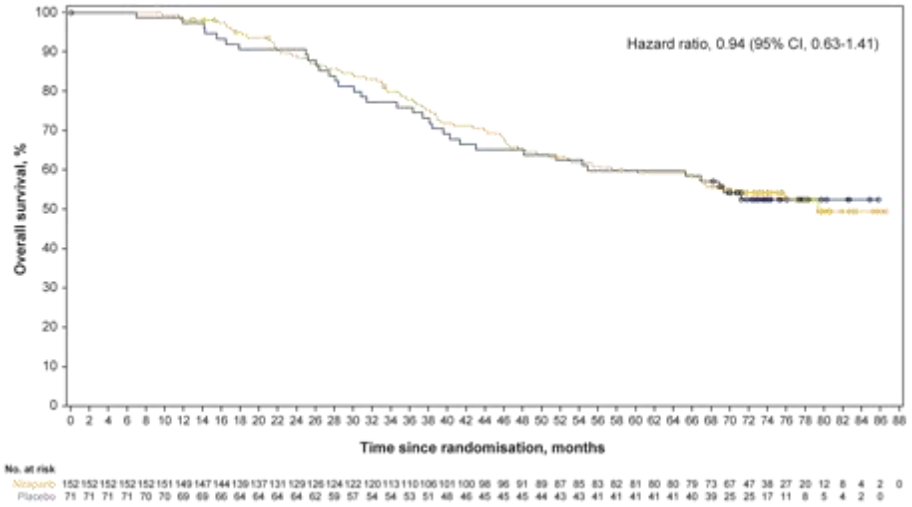
HRd



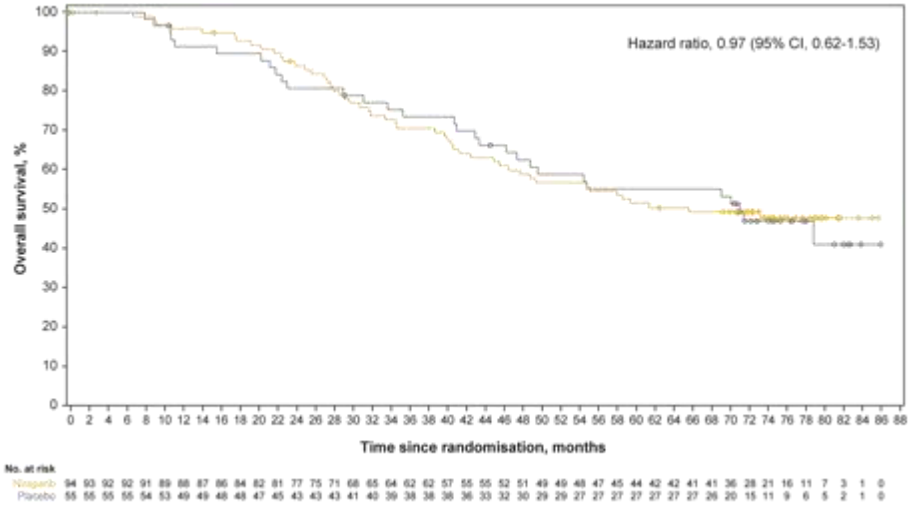
HRp



BRCAm



HRd/BRCAwt



62.5% maturity in overall population.

1. Monk B, et al. *Ann Oncol.* 2024;35(11):981–992.

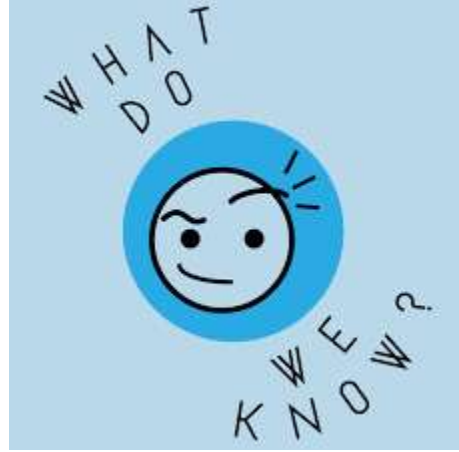
*BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild type;
CI, confidence interval; HR, hazard ratio;
HRd, homologous recombination deficient;
HRp, homologous recombination proficient; OS, overall survival.

Why PRIMA did not show overall survival benefit? Just few hypotheses

- Different population
  - Are PARP-i more effective in case of Primary debulking surgery with no residual disease ?
- Control arm: bevacizumab versus placebo
- Safety and dose intensity of PARP-i
- Progression during PARPi maintenance (more than 90% during PARPi in PRIMA versus 35% in PAOLA-1)
- Role of subsequent therapies
  - Surgery post progression 15.8% in PRIMA
  - Bevacizumab 35.8% PRIMA and 14.8% PAOLA-1

The benefit of PARPi in front line is not under discussion: PARPi maintenance remains standard of care at least in BRCAm and HRD pos tumors

What do we know?

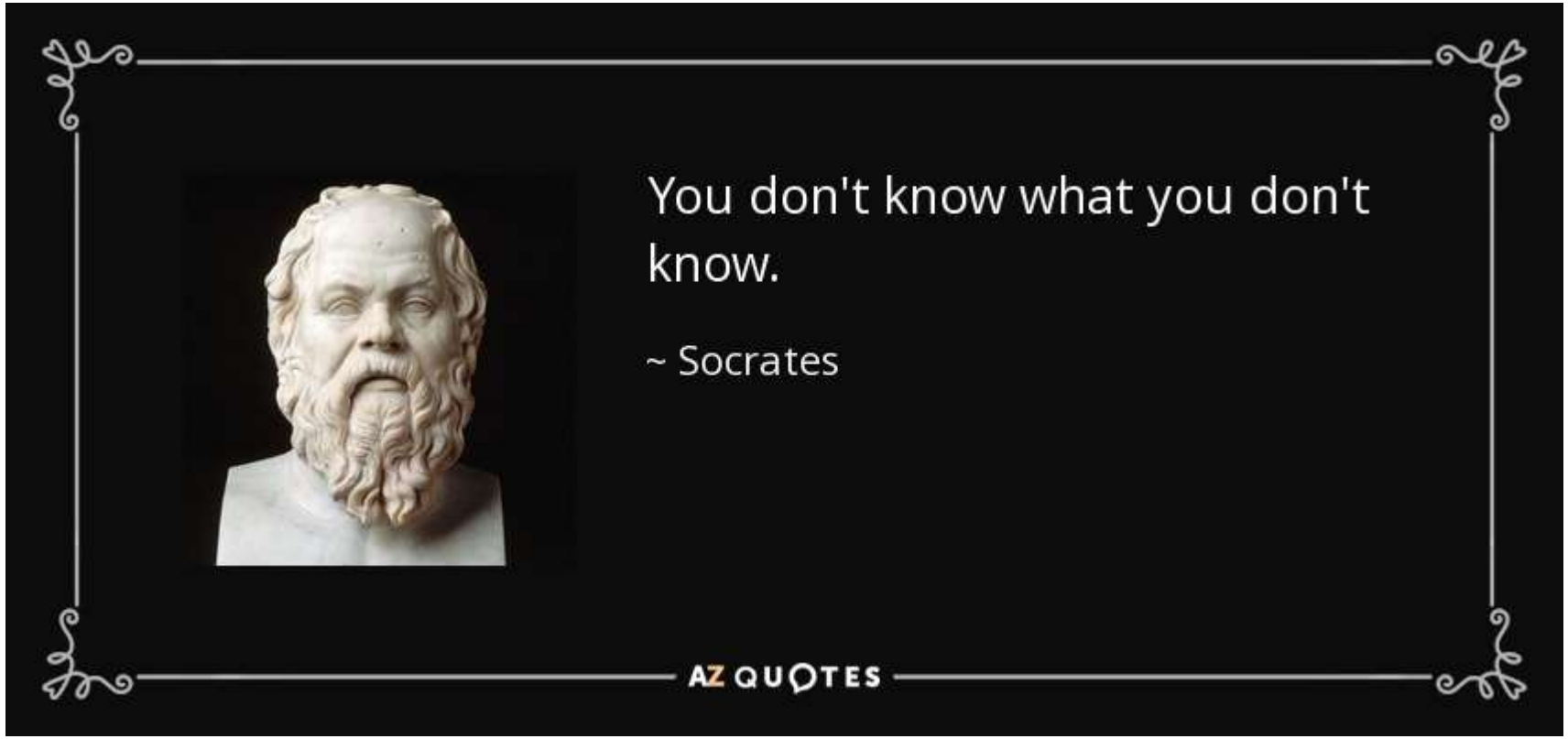


- All patients should be tested for BRCA and HRD
- All patients with BRCAm and/or HRD+ test must receive a parp inhibitor as maintenance after response to platinum-based chemotherapy
- Improvement in Overal survival in SOLO1 (BRCAm) and PAOLA 1 (HRD+)

What do we know?

- All patients should be tested for BRCA and HRD
- All patients with BRCAm and/or HRD+ test must receive a parp inhibitor as maintenance after response to platinum-based chemotherapy
- Improvement in Overal survival in SOLO1 (BRCAm) and PAOLA 1 (HRD+)
- The addition of IO does not improve outcome

What don’t we know?



What don’t we know?

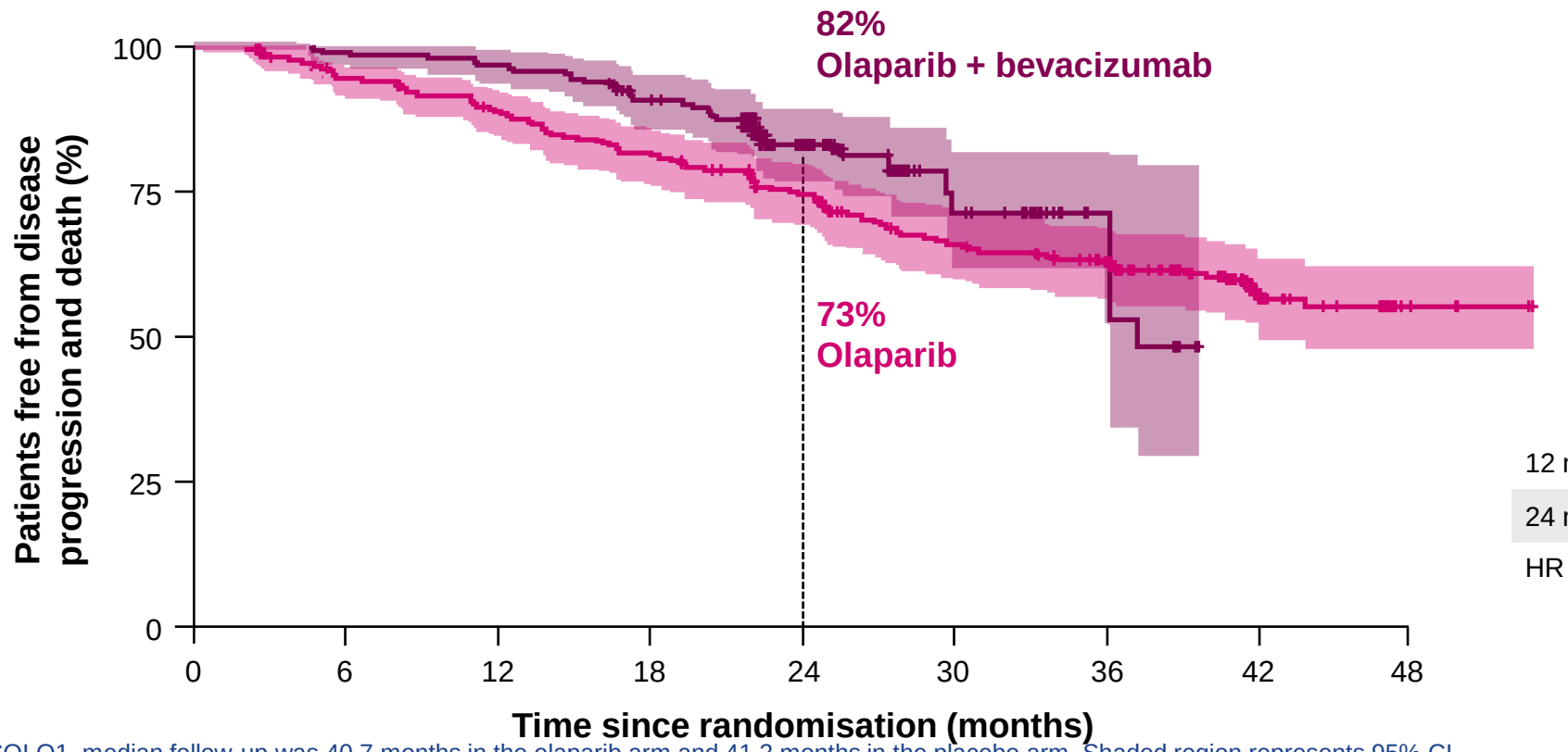
PARP-i alone vs PARP-i+Bevacizumab vs Bevacizumab maintenance ?

Patients with BRCAm or HRD must receive maintenance with PARP-i

Patients with BRCAm

Should we add bevacizumab?

A population-adjusted indirect treatment comparison of PAOLA-1 and SOLO1 showed an additive benefit from bevacizumab



Kaplan-Meier estimate of % of patients progression-free

	PAOLA-1 tumour *BRCA*m	SOLO1
	Olaparib + bevacizumab* n=151	Olaparib n=254
12 months	**96**	**88**
24 months	**82**	**73**
HR (95% CI)	**0.71 (0.45-1.09)†**	

In SOLO1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. Shaded region represents 95% CI.
In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm.
*These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (PDS vs IDS), residual disease status after surgery, response to first-line treatment and age to SOLO1. †CIs generated by bootstrapping. *BRCA*, breast cancer susceptibility gene; *BRCA*m, *BRCA* mutation; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IDS, interval debulking surgery; PDS, primary debulking surgery.
Vergote I, et al. *Eur J Cancer*. 2021;157:415-423.

Patients with BRCAm or HRD must receive maintenance with PARP-i

Patients with HRD positive tumor

Should we add bevacizumab?

Cross-trial comparison is challenging due to differences in the studied patient populations

Risk factor for progression of disease[a,1]	PRIMA[2] (niraparib)	PAOLA-1[3] (olaparib)	ATHENA-MONO[4] (rucaparib)	SOLO1[5] (olaparib)
Stage IV disease	35%	30%	25%	17%
BRCA wild type	70%	71%	79%	0%
Neoadjuvant chemotherapy	67%	42%	51%	35%
Partial response to chemotherapy	31%	27%	18%	18%
Visible residual disease	47%	40%	25%	23%

KEY: Clinical risk

Platinum sensitivity				
Response to platinum-based ChT				
CR/PR	100%	46%	35%	100%
NED	0%	54%	52%[b]	0%
Patients with PR and residual tumour >2 cm	Excluded	Included	Included	Included
Normalisation of CA-125 >90%	Required	Not required	Not required	Not required

KEY: Platinum sensitivity

Please note that head-to-head studies were not conducted between these products.
These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

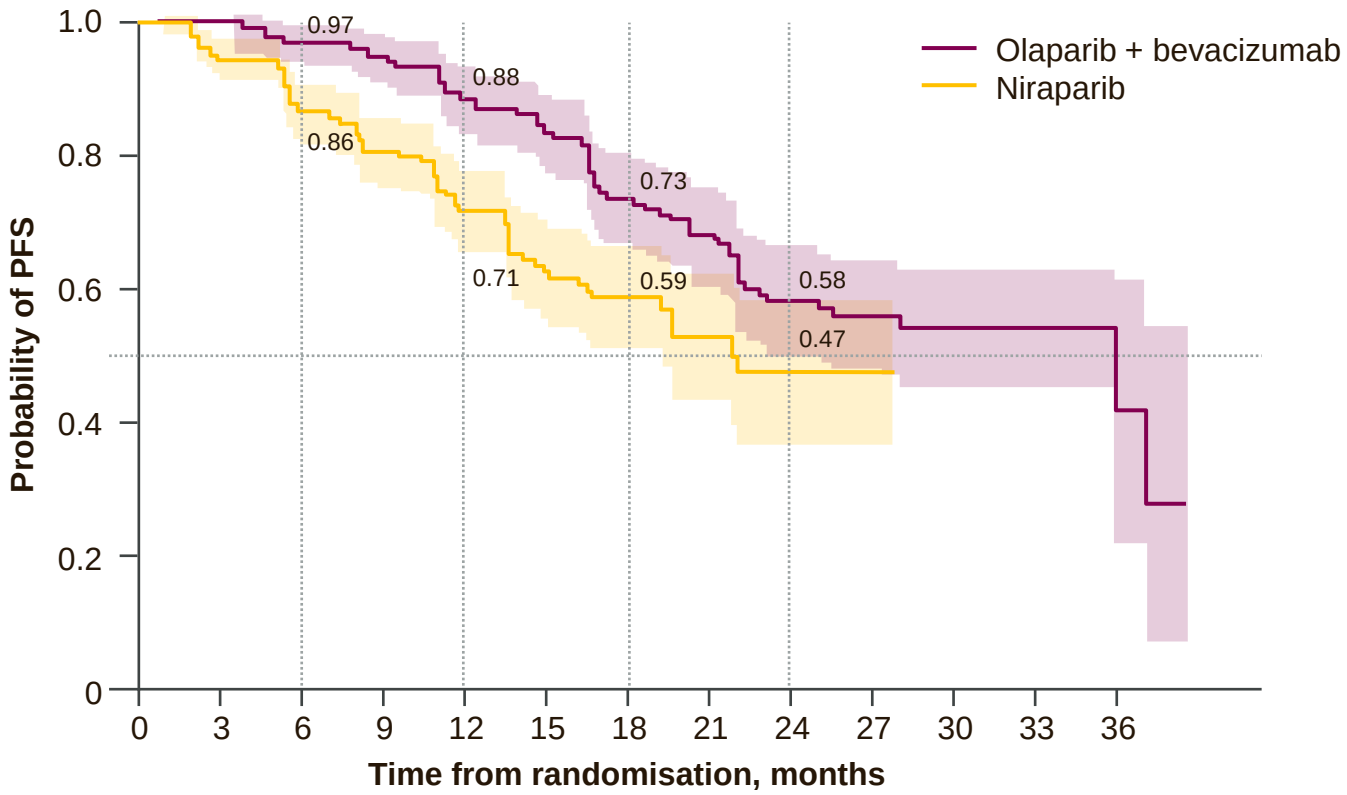
[a]Risk classification based on known risk factors for progression of advanced ovarian cancer: disease stage, therapy modality, visible residual disease after surgery and *BRCA* mutation status. [b]13% not evaluable/other.

CA-125, cancer antigen-125; ChT, chemotherapy; CR, complete response; NED, no evidence of disease; PR, partial response.

1. Chase D, et al. *JCO Clin Cancer Inform*. 2023;7:e2200189; 2. González-Martín A, et al. *N Engl J Med*. 2019;381:2391–402; 3. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2146–28; 4. Monk B, et al. *J Clin Oncol*. 2022;40(34):3952–3964; 5. Moore K, et al. *N Engl J Med*. 2018;379(26):2495–2505.

Indirect treatment comparison using propensity score weighting showed greater PFS benefit with olaparib + bevacizumab in HRD-positive[a] PAOLA-1 (PRIMA-eligible subset)[b] vs niraparib PRIMA patients

The PAOLA-1 cohort who were eligible for PRIMA were adjusted to match the baseline characteristics of the PRIMA patient population



	PAOLA-1 (PRIMA-eligible subset)[b]	PRIMA
	Olaparib + bevacizumab (ESS=164)	**Niraparib** (n=247)
Median PFS, months	36.0	22.0
PFS rates at 12 months, %	88	71
PFS rates at 24 months, %	58	47

HR 0.57
(95% CI, 0.41–0.79)

PAOLA-1 results based on individual patient data with outcomes weighted after matching FIGO stage, ECOG PS status, age, response to first-line chemotherapy, *BRCA*m status, HRD status, CA-125 levels and use of NACT to the PRIMA baseline characteristics. PRIMA dataset was reconstructed using published PFS curves.[1]

[a]HRD-positive defined as *BRCA*m and/or genomic instability score ≥42 in the Myriad myChoice® CDx assay.[2,3]

[b]Patients with stage IV disease, stage III with residual disease after primary debulking surgery, inoperable stage III disease, or stage III who received NACT.[1]

*BRCA*m, *BRCA* mutated; CA-125, cancer antigen-125; CDx, companion diagnostic; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; FIGO, International Federation of Gynaecology and Obstetrics; HR, hazard ratio; HRD, homologous recombination deficiency; NACT, neoadjuvant chemotherapy; PFS, progression-free survival.

1. Hettle R, et al. *Ther Adv Med Oncol*. 2021;13:17588359211049639; 2. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2146–28; 3. González-Martín A, et al. *N Engl J Med.* 2019;381:2391–402.

Patients with BRCAm or HRD must receive maintenance with PARP-i

Patients with HRD positive tumor

Should we add bevacizumab?

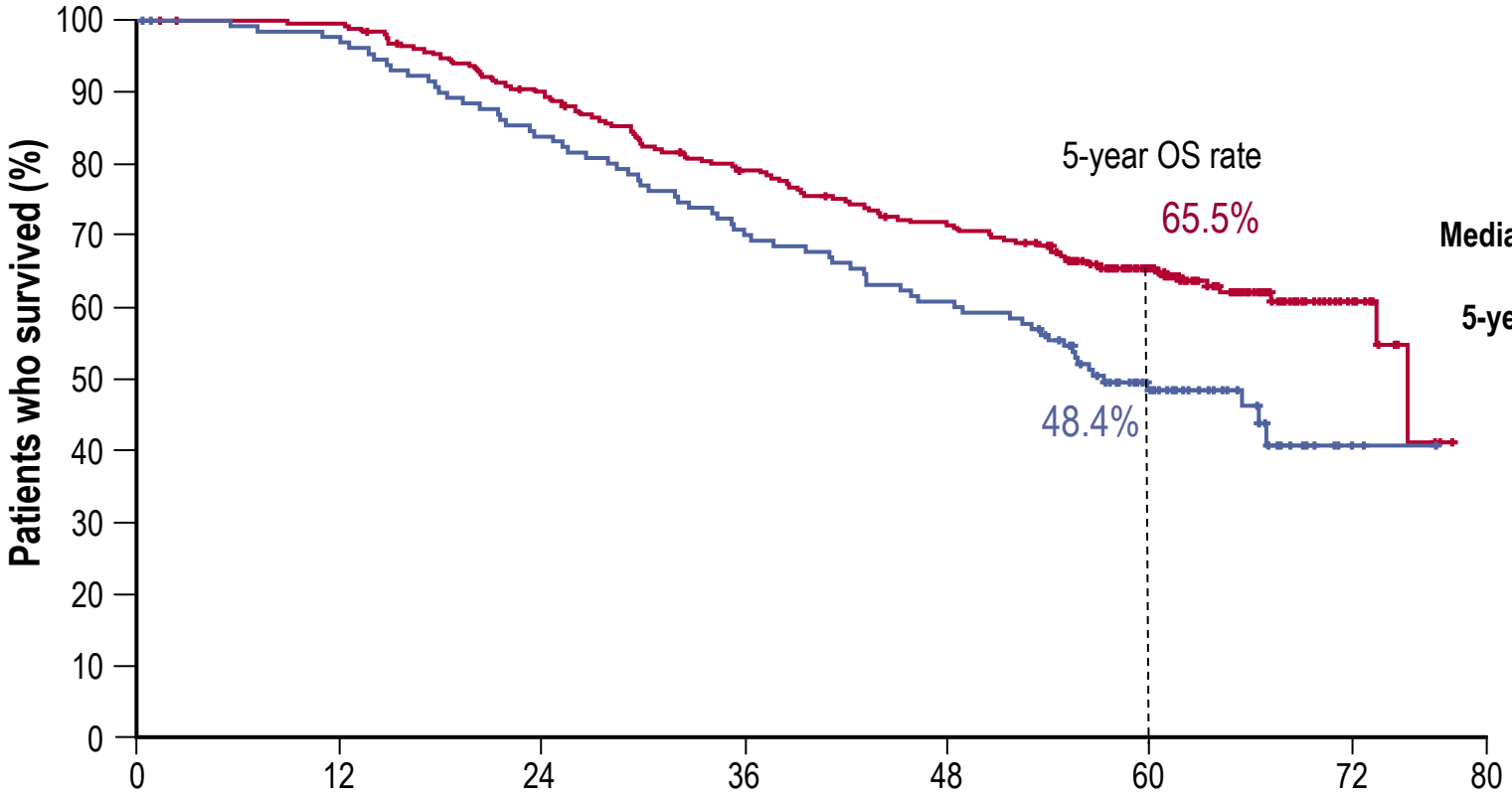
Overall Survival Data?

Clinical characteristics(stage and residual tumor)?

Response to chemotherapy?

Toxicity and quality of life/patient preference ?

Paola 1:
OS was prolonged in the HRD-positive subgroup



	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)

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

*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.

Isabelle Ray-Coquard, ESMO 2022

This study was supported by AstraZeneca

Patients with BRCAm or HRD must receive maintenance with PARP-i

Patients with HRD positive tumor

Should we add bevacizumab?

Survival Data?

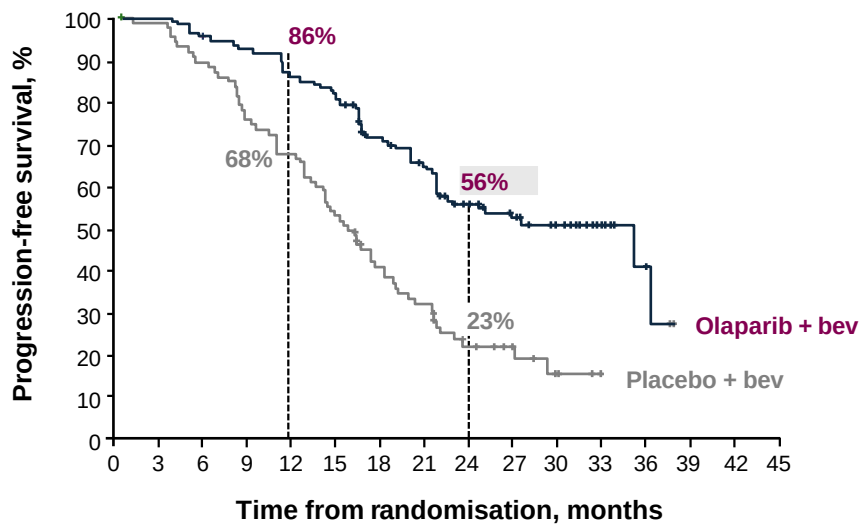
Clinical characteristics(stage and residual tumor)?

Response to chemotherapy?

Toxicity and quality of life/patient preference ?

In PAOLA-1, PFS benefit was seen in HRD-positive patients regardless of clinical risk

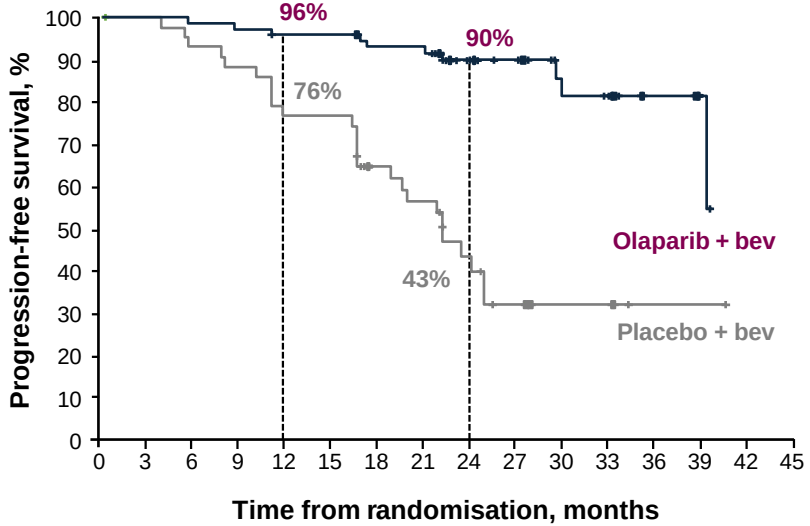
Higher risk, HRD-positive population



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

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

Lower risk, HRD-positive population



Patients at risk, n															
Olaparib + bev	78	77	76	75	73	73	60	60	40	35	19	14	6	3	0
Placebo + bev	43	42	39	37	32	32	23	20	12	7	3	3	1	1	0

	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)	

[a]Unstable median due to lack of events.

Higher-risk patients 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. Lower-risk patients were those with FIGO stage III disease who had undergone upfront surgery and had complete resection.

bev, bevacizumab; CI, confidence interval; FIGO, International Federation of Gynaecology and Obstetrics; HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.

Harter P, et al. *Gynecol Oncol*. 2022;164(2):254–264.

Patients with BRCAm or HRD must receive maintenance with PARP-i

Patients with HRD positive tumor

Should we add bevacizumab?

Survival Data?

Clinical characteristics(stage and residual tumor)?

Response to chemotherapy?

Toxicity and quality of life/patient preference ?

Response to chemotherapy predict outcome with PARP-i

	PRIMA[a] Niraparib	PAOLA-1[b] Olaparib + Bevacizumab
Prior surgical status	▪ Stage III PDS with residual disease ▪ Stage III IDS / stage IV	▪ No limitation
Response criteria	▪ CR/PR (investigator) AND ▪ All Stage III PDS patients **had measurable disease** to assess platinum response ▪ PR > 2 cm excluded ▪ **Normal or > 90% ↓ CA-125** ▪ CR rate after chemotherapy: 69%	▪ CR/PR (investigator) ▪ CR rate after chemotherapy: 20% ▪ **Response partially based on bevacizumab** ▪ **50% PDS & 60% RD = 0 mm**
Control arm	▪ Placebo	▪ Placebo + bevacizumab
Duration of PARP inhibitor maintenance	▪ 3 years	▪ 2 years
Primary endpoint	▪ PFS by BICR ▪ Stratification factors: HRD positive (including *BRCA* mutated) vs other; CR/PR; NACT	▪ Investigator-assessed PFS (ITT) ▪ Stratification factors: *BRCA* mutated vs negative/unknown; NED/CR/PR
Follow-up duration	▪ 13.8 months	▪ 24.0 months
Scanning schedule	▪ Every 12 weeks	▪ Every 24 weeks (every 12 weeks if CA-125 elevated)

STRONG selection for evaluable response to platinum

Response to platinum less certain

a. Gonzalez-Martin A, et al. N Engl J Med 2019;381:2391–2402; b. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–2428.

Modeled CA-125 ELIMination rate constant K (KELIM) & bevacizumab benefit in GOG-218
FIGO stage IV and Stage III with VRD > 1 cm after PCS

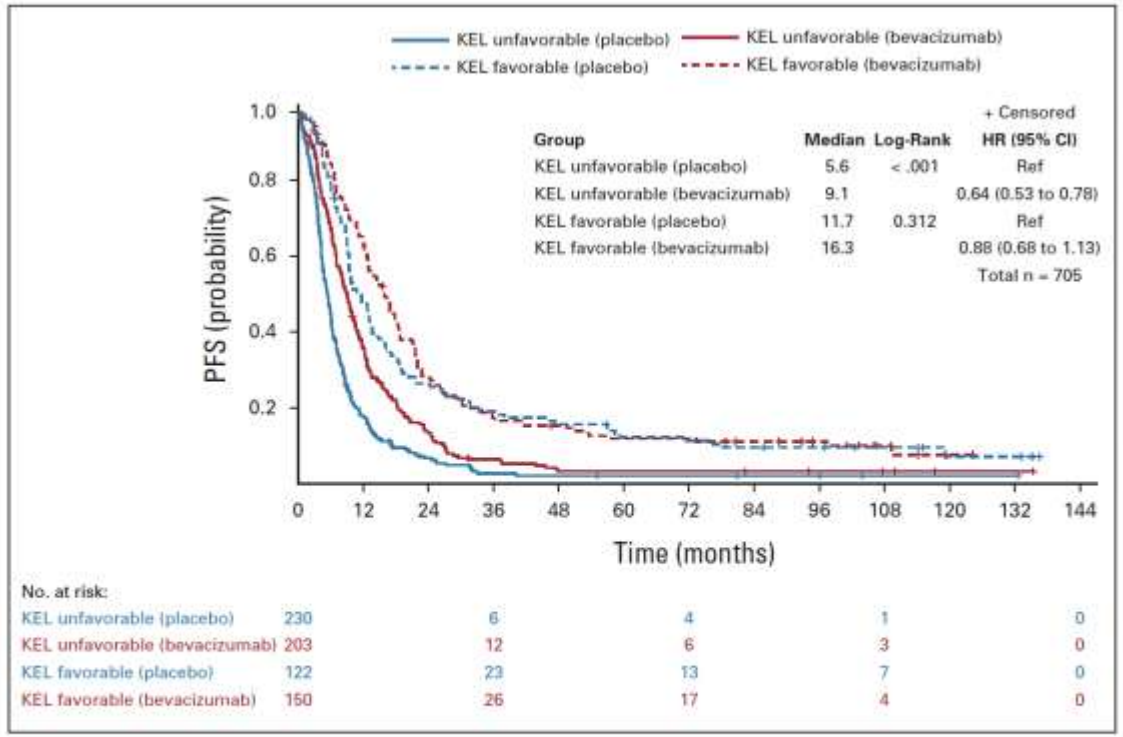


FIG 3. Kaplan-Meier curves of the PFS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); PFS, progression-free survival; Ref, reference.

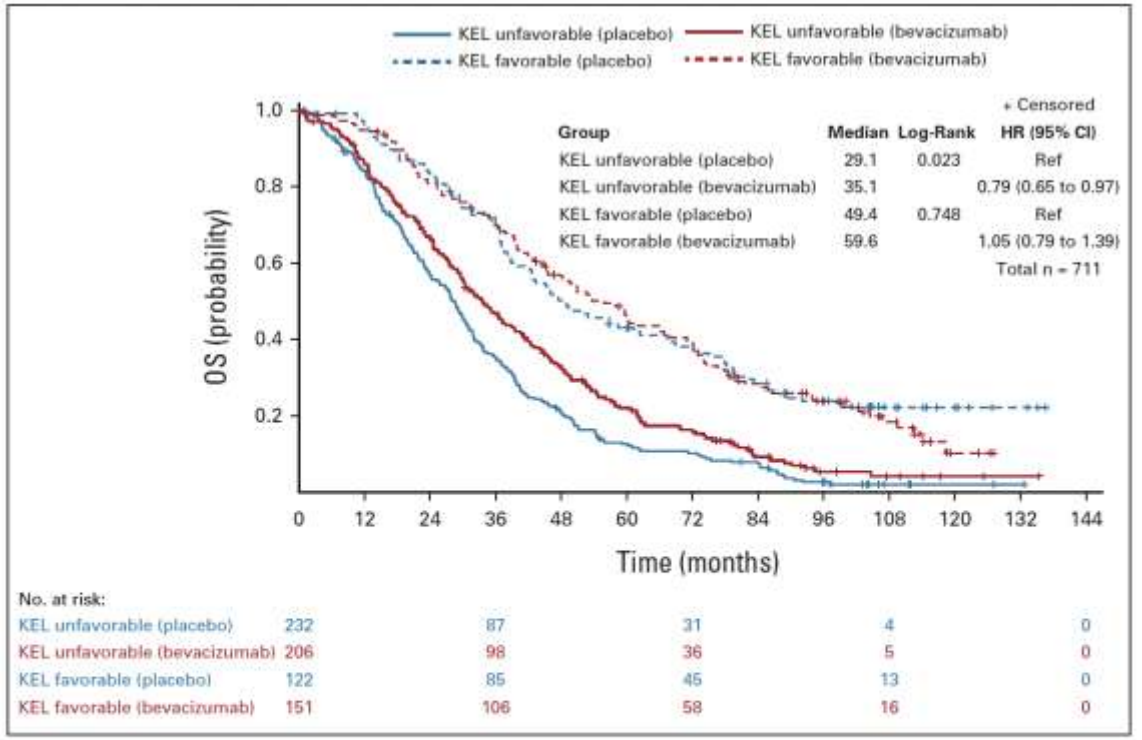
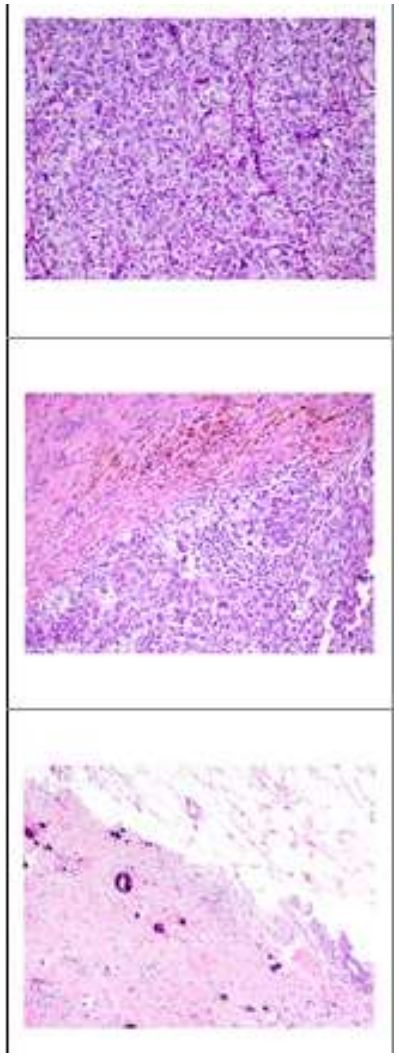


FIG 4. Kaplan-Meier curves of the OS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); OS, overall survival; PFS, progression-free survival; Ref, reference.

You et al. J Clin Oncol 2022 , Oct 17:JCO2201207. doi: 10.1200/JCO.22.01207

How Much platinum sensitive is this tumor?

The chemotherapy response score (CRS)



- **CRS score 1: No or minimal tumour response** (mainly viable tumour with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci)

- **CRS score 2: Appreciable tumour response with residual tumour**, (ranging from multifocal or diffuse fibro-inflammatory regressive changes, with tumour in sheets, streaks or nodules, to extensive regression associated fibro-inflammatory changes with multifocal residual tumour which is **regularly** distributed and easily identifiable)

- **CRS score 3: Complete or near-complete response** (mainly regression associated fibro-inflammatory changes with minimal i.e. very few, **irregularly** scattered individual tumour cells or cell groups or nodules up to 2mm OR no residual tumour identified)

Steffen Böhm 2015 Aug 1;33(22):2457-63

Patients with BRCAm or HRD must receive maintenance with PARP-i

Patients with HRD positive tumor

Should we add bevacizumab?

Survival Data?

Clinical characteristics(stage and residual tumor)?

Response to chemotherapy?

Toxicity and quality of life/patient preference ?

Safety profile across first-line maintenance trials: Summary

	SOLO1[a,1,2]		PAOLA-1[b,3]		PRIMA[c,4]			ATHENA-MONO[5]	
	Olaparib	Placebo	Olaparib + bev	Bev + placebo	Niraparib (Overall)	Niraparib FSD | ISD	Placebo	Rucaparib	Placebo
N	260	130	535	267	484	313 | 169	244	425	110
AE leading to dose reduction, %	**28.8**	3.1	**41.0**	7.0	**71.7**	**76.5 | 62.7**	10.2	**49.4**	8.2
AE leading to dose interruption, %	**52.7**	16.9	**54.0**	24.0	**80.8**	**84.8 | 73.4**	23.0	**60.7**	20.0
AE leading to discontinuation, %	11.9	3.1	20.0	6.0	16.3	14.9 | 18.9	3.7	11.8	5.5
Grade ≥3 AEs, %	39.6	20.0	57.0	51.0	73.8	79.0 | 63.9	23.8	60.5	23.6

SOLO1 data from 7-year descriptive OS analysis; PAOLA-1 data from primary analysis; PRIMA data from 5-year final OS analysis; ATHENA-MONO from primary analysis.

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. Cross-trial comparisons are not head-to-head studies; varying study designs, methodology and populations limit ability to draw conclusions of comparative efficacy and safety.

Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.

[a]Median follow-up of 89 months for olaparib and 87 months for placebo. [b]Median follow-up of 24 months in the olaparib arm and 23 months in the placebo arm. [c]In both arms, median follow-up of 6.2 years.

AE, adverse event; AML, acute myeloid leukaemia; bev, bevacizumab; FSD, fixed starting dose; ISD, individualised starting dose; MDS, myelodysplastic syndrome; OS, overall survival.

1. DiSilvestro P, et al. *J Clin Oncol*. 2023;41(3):609–617; 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(25):2416–2428;
4. Monk BJ, et al. *Ann Oncol*. 2024;35(11):981–992; 5. Monk BJ, et al. Presented at: ASCO Annual Meeting; 3–7 June 2022; Chicago, IL, USA [Abstract LBA5500].

Safety profile across first-line maintenance trials: Summary

	SOLO1[a,1]		PAOLA-1[b,2]		PRIMA[c,3]			ATHENA-MONO[4]	
	Olaparib	Placebo	Olaparib + bev	Bev + placebo	Niraparib (Overall)	Niraparib FSD | ISD	Placebo	Rucaparib	Placebo
n	260	130	535	267	484	313 | 169	244	425	110
Grade ≥3 AEs, %	39.6	20.0	57.0	51.0	73.8	79.0 | 63.9	23.8	60.5	23.6
Thrombocytopenia	0.8	1.5	2.0	<1.0	39.9	49.2 | 22.5	<1	7.1	0.0
Anaemia	21.9	1.5	17.0	<1.0	32.0	36.5 | 23.7	2.0	28.7	0.0
Neutropenia	8.5	4.6	6.0	3.0	21.3	24.8 | 14.8	1.6	14.6	0.9
Hypertension	NR	NR	19.0	30.0	7.2	8.3 | 5.3	2.0	NR	NR
Fatigue	3.8	1.5	5.0	1.0	2.3	2.2 | 2.4	0.4	NR	NR
Insomnia	0.0	0.0	NR	NR	1.0	1.6 | 0.0	0.4	0.2	0.0
Nausea	0.8	0.0	2.0	1.0	1.2	1.3 | 1.2	0.8	1.9	0.0
Diarrhoea	3.1	0.0	2.0	2.0	0.8	0.3 | 1.8	0.4	1.4	0.9
Constipation	0.0	0.0	0.0	<1.0	0.4	0.3 | 0.6	0.0	0.0	0.0
AML/MDS, %	1.5	0.8	1.7	2.2	2.3	NR	1.6	0.5	0.0
New primary malignancies, % Breast Cancer	5.4 3.8	6.2 3.8	4.1[5] 2.1[5]	3.0 1.5	2.5 NR	NR	2.5 NR	NR	NR

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. Cross-trial comparisons are not head-to-head studies; varying study designs, methodology and populations limit ability to draw conclusions of comparative efficacy and safety. [a]Median follow-up of 89 months for olaparib and 87 months for placebo. [b]Median follow-up of 24 months in the olaparib arm and 23 months in the placebo arm. [c]In both arms, median follow-up of 6.2 years.

AE, adverse event; AML, acute myeloid leukaemia; bev, bevacizumab; FSD, fixed starting dose; ISD, individualised starting dose; MDS, myelodysplastic syndrome; NR, not reported; OS, overall survival. 1. DiSilvestro P, et al. *J Clin Oncol*. 2023;41(3):609–617; 2. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416–2428; 3. Monk BJ, et al. *Ann Oncol*. 2024;35(11):981–992; 4. Monk BJ, et al. *J Clin Oncol*. 2022;40(34):3952-3964; 5. Ray-Coquard I, et al. Ann Oncol 2023;34(8):681–692

No randomised clinical trial data are yet available to directly demonstrate the efficacy contribution of bevacizumab to 1L PARPi maintenance

No olaparib monotherapy arm in

PAOLA-1[1]

PARPi monotherapy

SOLO1[2]

PRIMA[3]

ATHENA-MONO[,4]

Ongoing trials will allow a direct comparison of 1L PARPi with and without bevacizumab

NIRVANA-1[5]	AGO-OVAR 28[6]	MITO25[7]
Niraparib ± bevacizumab as maintenance after complete cytoreduction	Niraparib vs niraparib + bevacizumab as maintenance after platinum + bevacizumab	Chemotherapy ± bevacizumab followed by rucaparib maintenance ± bevacizumab or bevacizumab alone

But what evidence is available to guide clinical practice for today?

1L, first line; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor.

1. Ray Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428; 2. Moore K, et al. *N Engl J Med.* 2018;379(26):2495-2505; 3. González Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402; 4. Monk BJ, et al. *Int J Gynecol Cancer.* 2021;31(12):1589-1594; 5. ClinicalTrials.gov. NCT0518398; 6. ClinicalTrials.gov. NCT05009082; 7. ClinicalTrials.gov. NCT03462212. ClinicalTrials.gov website accessed 29 June 2024.

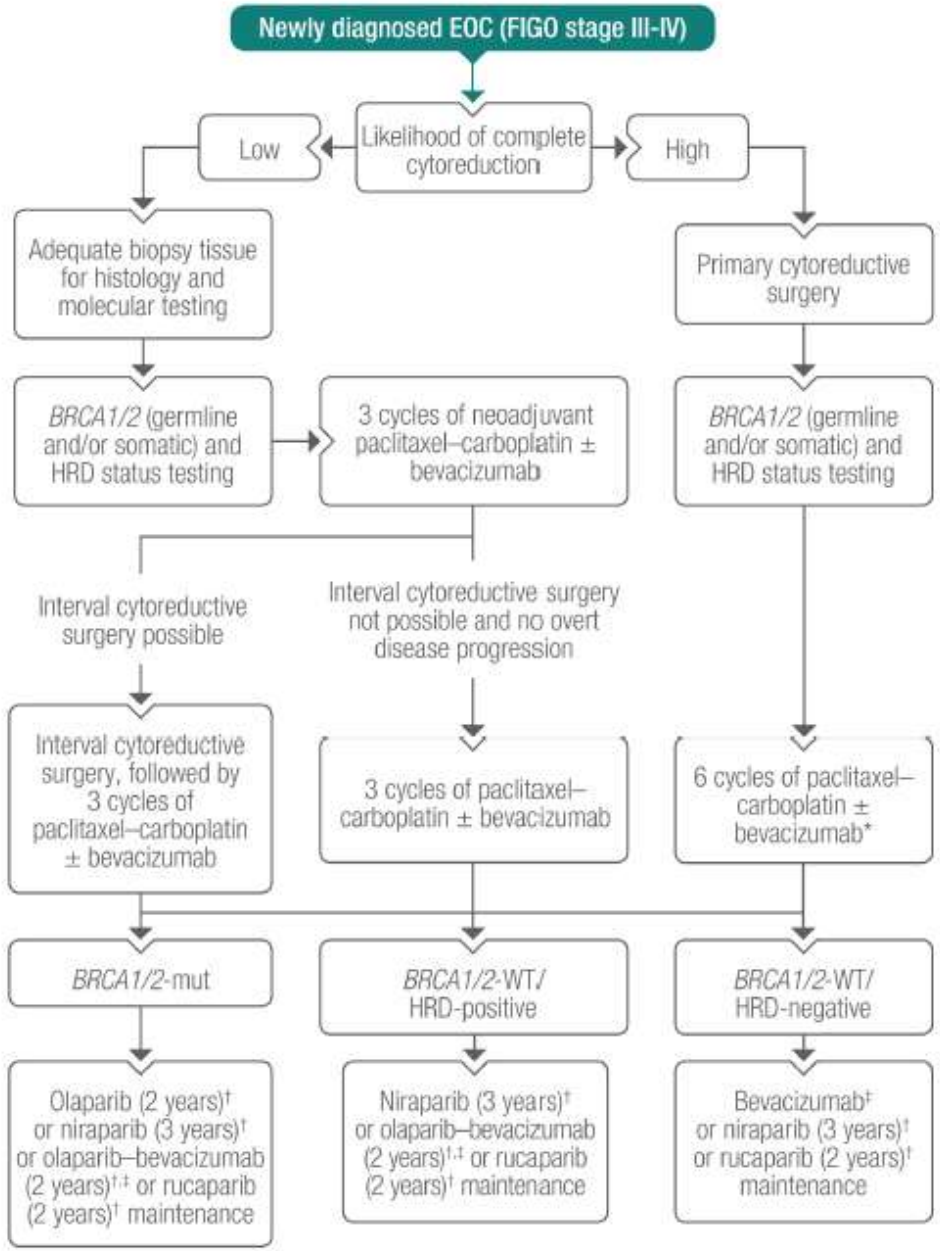
What don’t we know?

For patients with HRD-negative test, should we use PARPi or bevacizumab?

ESMO POCKET GUIDELINES

BRCA1/2-WT/
HRD-negative

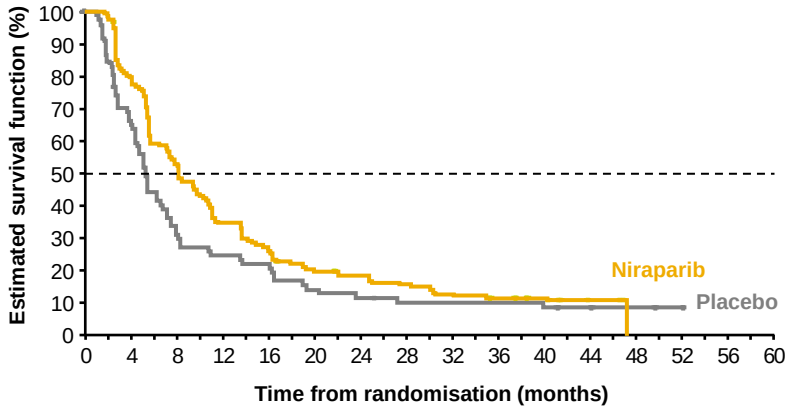
Bevacizumab‡
or niraparib (3 years)†
or rucaparib (2 years)†
maintenance



In patients with HRD-negative status, 1L PARPI maintenance has shown limited efficacy and the combination of PARPi plus bevacizumab no benefit versus bevacizumab alone

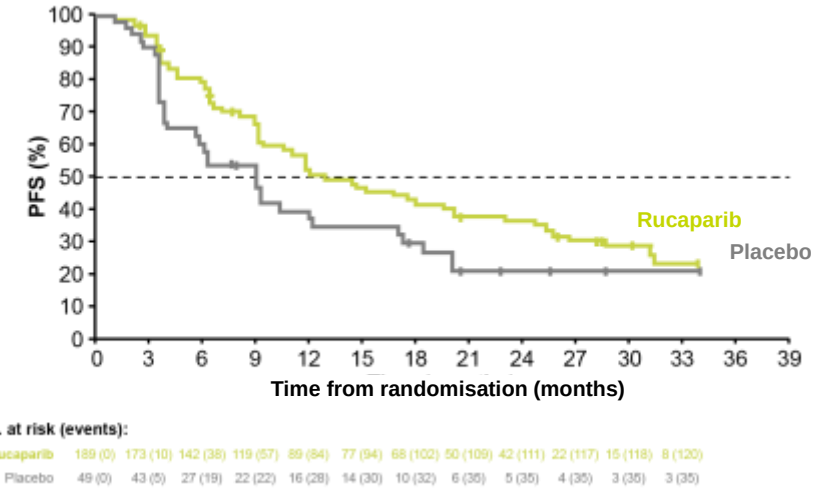
PARPi monotherapy *versus* watch and wait

PRIMA (PFS, HRD negative)[1]



	Niraparib	Placebo
mPFS, months	**8.4**	**5.4**
	HR 0.65 (95% CI, 0.49-0.87)	

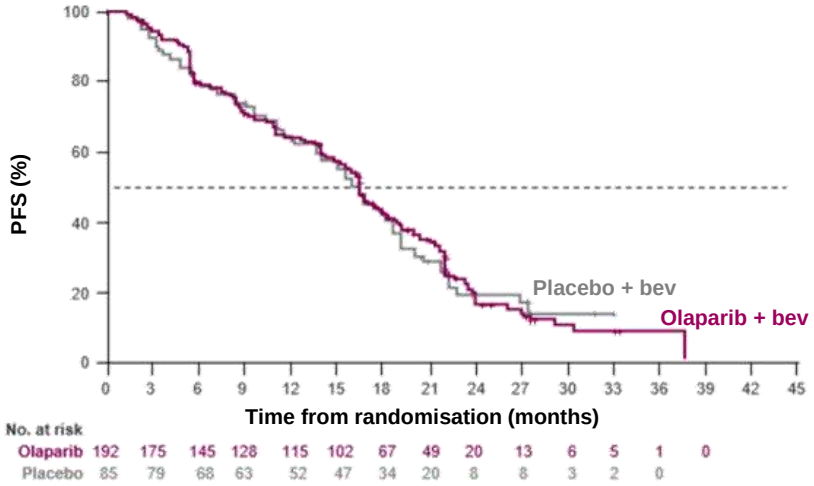
ATHENA-MONO (PFS, HRD negative)[2]



	Rucaparib	Placebo
mPFS, months	**12.1**	**9.1**
	HR 0.65 (95% CI, 0.45-0.95)	

Olaparib plus bev combination *versus* bev maintenance

PAOLA-1 (PFS, HRD negative)[3]



	Olaparib + bev	Placebo + bev
mPFS, months	**16.6**	**16.2**
	HR 1.00 (95% CI, 0.75-1.35)	

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended

1L, first-line; bev, bevacizumab; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; mPFS, median PFS; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor; PFS, progression-free survival.

1. Gonzalez-Martin A, et al. Poster presented at: ESMO 2022. Abstract 530P; 2. Monk BJ, et al. *J Clin Oncol.* 2022;40(34):3952-3964 3. Ray-Coquard I, et al. Presented at: ESMO 2022. Abstract LBA29.

Lessons after 5 years of PARPi in HRD-negative (HRp)

90% of HRD-negative (HRp) patients relapse at 3 years

PAOLA-1 (ITT)

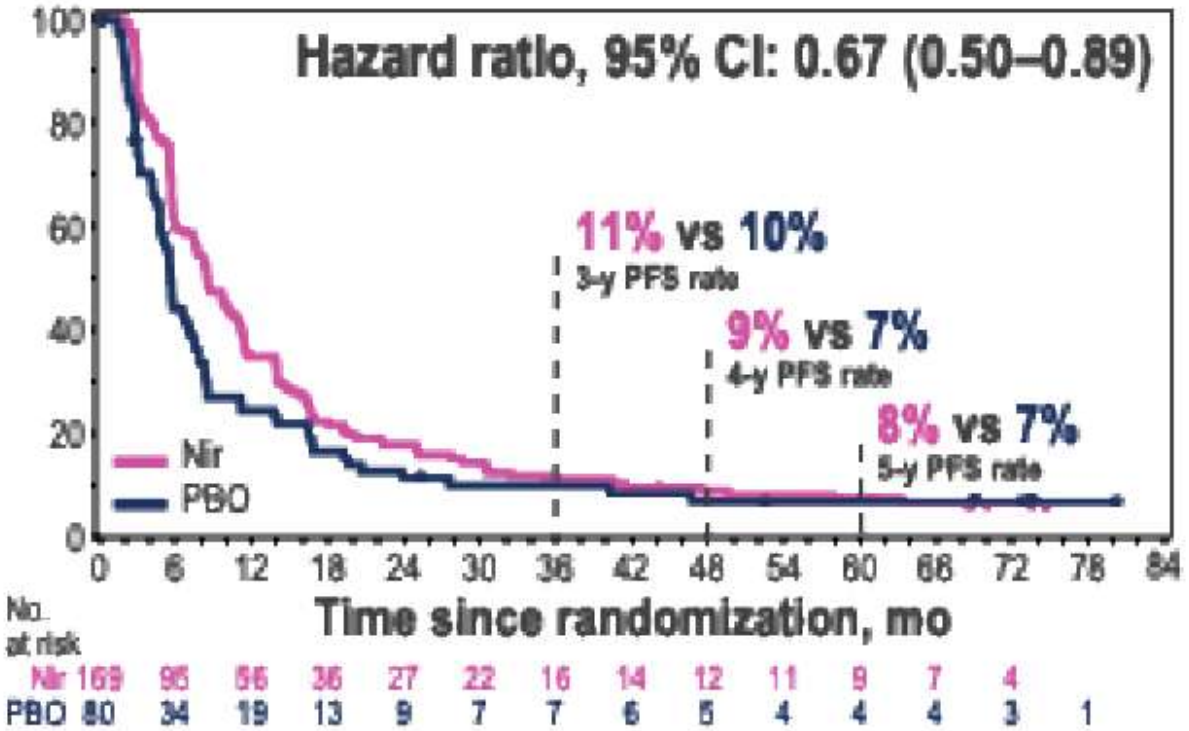
Table 2. Updated analysis of progression-free survival by molecular subgroups

PFS[a]	HR (95% CI)	5-Year PFS rate (%)	
		Olaparib plus bevacizumab	Placebo plus bevacizumab
HRD-negative/unknown	0.9 (0.72-1.13)	13.4	12.6
HRD-negative	1.01 (0.77-1.33)	8.0	11.7
HRD unknown	0.69 (0.47-1.03)	24.4	14.3

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NE, not estimated; PFS, progression-free survival; tBRCAm, tumor *BRCA1/BRCA2* mutation.
[a]Descriptive analysis; PFS by investigator assessment (modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1).

Adapted from Ray-Coquard et al. Ann Oncol 2023
https://doi.org/10.1016/j.annonc.2023.05.005

PRIMA



Gonzalez-Martin et al. ESMO 2024 Proffered Paper Session
Monk et al. Ann Oncol 2024.
https://doi.org/10.1016/j.annonc.2024.08.2241

HRR deficiency testing in clinical trials

MyChoice® CDx
HRD Companion Diagnostic Test

FOUNDATIONONE® CDx

BGI ONCOLOGY

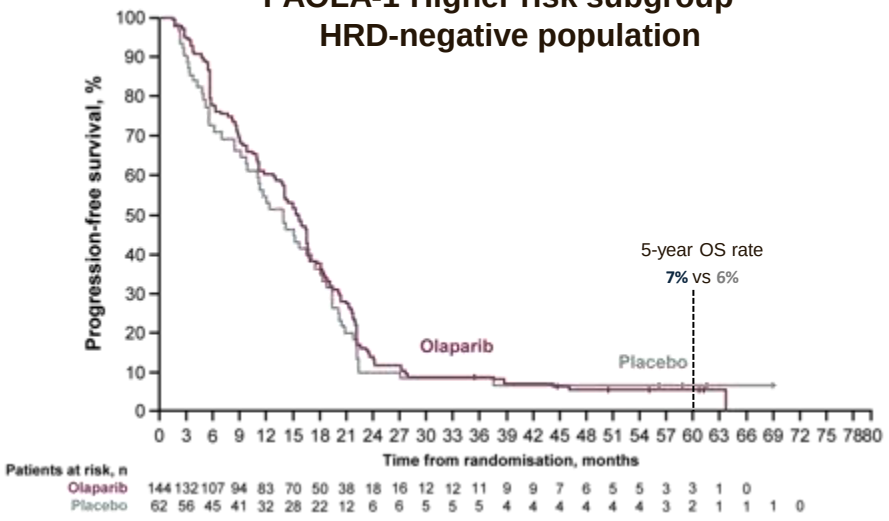
Test	Trial	Predictive	Prognostic
MyChoice	PAOLA-1	Yes	No
MyChoice	PRIMA	Partially	Yes
BGI	PRIME	No	Yes
FoundationOne	ATHENA	Partially	No

Imperfect “Gold-Standard”

Some tumor test negative but indeed they have a HR deficiency!!!
Current HRR deficiency tests are useful for selecting patients with HR deficient tumours for PARPi maintenance but are not good enough for ruling out the benefit of PARPi monotherapy in patients with HR-proficient tumours

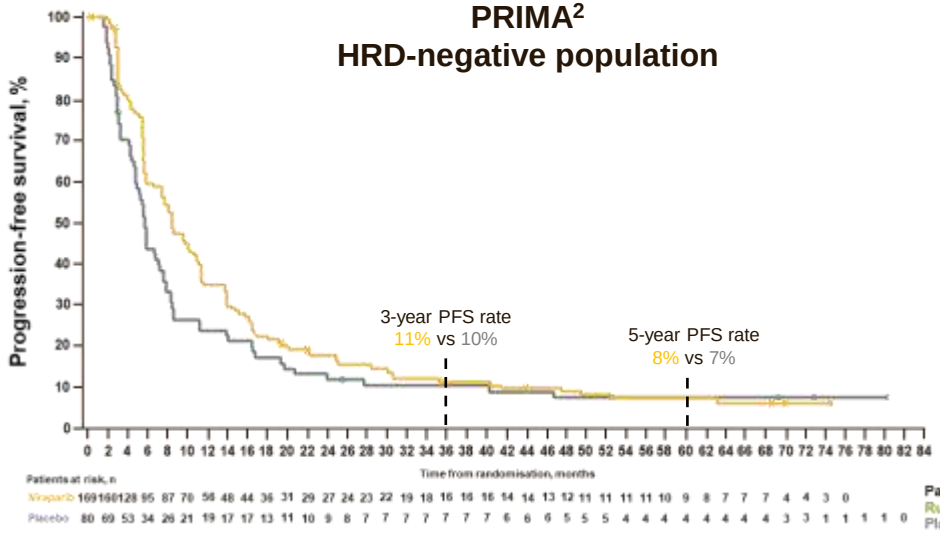
Median PFS in the control arm of PAOLA-1 among patients with higher risk, HRD-negative disease compared with that in the treatment arms of PRIMA and ATHENA-MONO

PAOLA-1 Higher risk subgroup[1a]
HRD-negative population



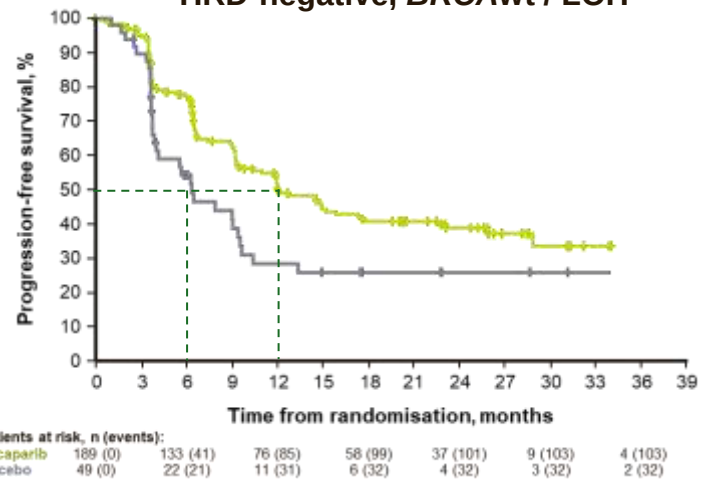
	Olaparib + bev (n=144)	Placebo + bev (n=62)
Events, n (%)	130 (90)	57 (92)
Median PFS, months	**15.2**	**13.8**
	HR 0.92 (95% CI, 0.68–1.27)	

PRIMA[2]
HRD-negative population



	Niraparib (n=169)	Placebo (n=80)
Events, n (%)	147 (87.0)	71 (88.8)
Median PFS, months	**8.4**	**5.4**
	HR 0.67 (95% CI, 0.50–0.89)	

ATHENA-MONO[3]
HRD-negative, *BRCA*wt / LOH[low]



	Rucaparib (n=185)	Placebo (n=49)
Median PFS, Months (95% CI)	**12.1**	**9.1**
	HR 0.65 (95% CI, 0.45–0.95)	

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

[a]Patients with Stage III OC who had residual disease following PDS, or those who had received neoadjuvant chemotherapy and/or those with Stage IV disease

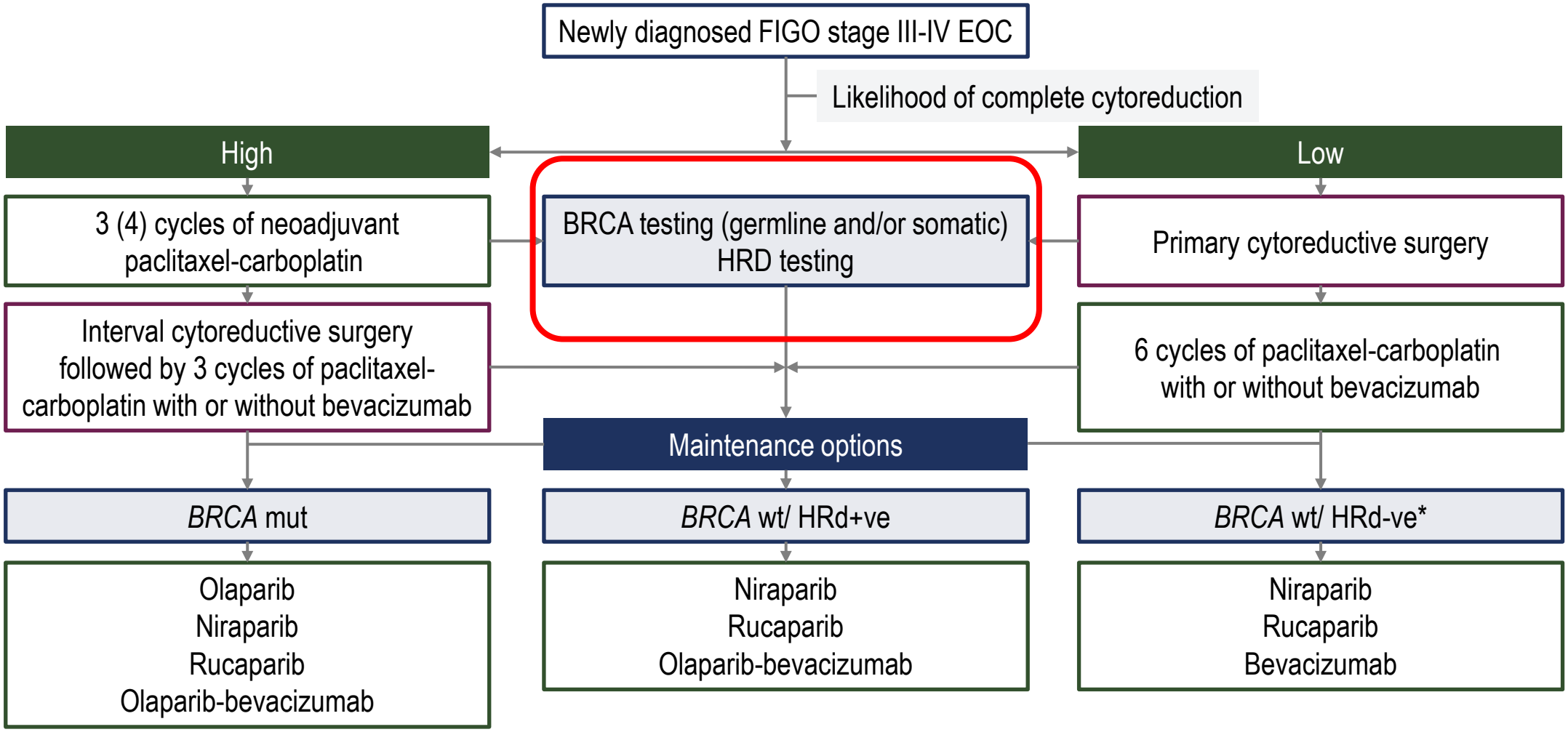
*BRCA*wt, *BRCA* wild-type; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; PFS, progression-free survival.

1. Lorusso D et al Int J Gynecol Cancer 2024;34:550–558; 2. Monk B, et al Ann Oncol. 2024;35(11):981–992; 3. Monk B, et al. *J Clin Oncol.* 2022;40(34):3952–3964

The ideal patient for PARP-i alone?

Good response to platinum

Management of Advanced FIGO Stage III-IV ovarian cancer- ESMO Guidelines

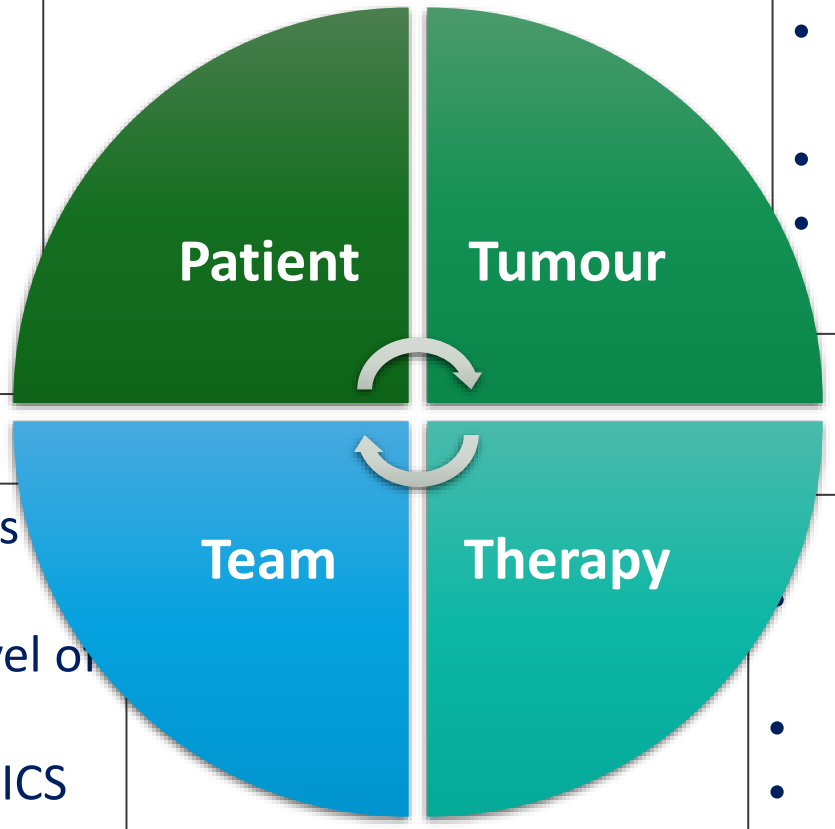


Gonzalez et al Ann Oncol 2023

The Complexity of Personalized Therapy: Addressing the Heterogeneity of AOC

- Age
- Performance status (ECOG)
- Co-morbidities
- Expectations
- Desires and own vision of life
- Caregivers' availability and support

- Histology
- BRCA y HRD status
- Other Genomics (CCNE1, RAD51,…)
- Tumour microenvironment
- Mechanisms of resistance to platinum and/or PARPi



- Pre-surgical assessment (CT vs PET vs laparoscopy)
- Skills of the surgical team (level of specialization)
- Residual tumour after PCS or ICS
- Surgical complications

Response to chemo (RECIST)
CA-125 kinetic of elimination (KELIM)
- Bevacizumab and / or PARPi
- Safety & profile of drugs
- Access and reimbursement

1. Caruso G, TomaoF, Parma G, et al. Poly(ADP-ribose)polymeraseinhibitors(PARPi) in ovariancancer:lessonslearnedand future directions.IntJ Gynecol Cancer. 2023;33(4):431–43 2. Mirza MR, Coleman RL, González-Martín A, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol. 2020;31(9):1148–59. 3. O'Cearbhaill RE. Using PARP inhibitors in advanced ovarian cancer. Oncology (Williston Park). 2018;32(7):339–43. 4. Havrilesky LJ, Lim S, Ehrisman JA, et al. Patient preferences for maintenance PARP inhibitor therapy in ovarian cancer treatment. Gynecol Oncol. 2020;156(3):561–7.

Take home message

- Maintenance therapy with PARP inhibitors in front line has changed the natural history of patients with HGSOC and GIS+ tumors
- BRCA and HRD Testing is mandatory for patient treatment selection
- Therapeutic management of ovarian cancer in multiple settings has shifted dramatically, with the first-line overall survival data from SOLO-1 and PAOLA-1 raising the hope of a potential cure
- The role of bevacizumab added to PARPi in patients with GIS tumors is still a matter of debate.
  - Clinical characteristics may not play a major role
  - Optimal Response to chemotherapy may favour PARP-i monotherapy
  - KELIM score can help select patients with the greater benefit from bevacizumab but randomized clinical trial are eagerly awaited
- New biomarkers beyond BRCA and GIS (such as ctDNA) are needed to identify patients that will progress on or shortly after PARPi
- Taken together, current evidence highlights the importance of introducing PARPi as early as possible for eligible patients