2025: NOVITA’ NEL TRATTAMENTO DELLE NEOPLASIE GINECOLOGICHE
VERONA 7 MARZO 2025

Nuovi approcci clinici nel carcinoma ovarico avanzato

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Ovarian cancer is a clinically aggressive disease

Ovarian cancer has the **highest mortality rate** of all gynecological cancers[1]

Over 300,000 patients estimated to be diagnosed with ovarian cancer each year[2]

Globally, ovarian cancer results in **over 200,000 deaths** each year[2]

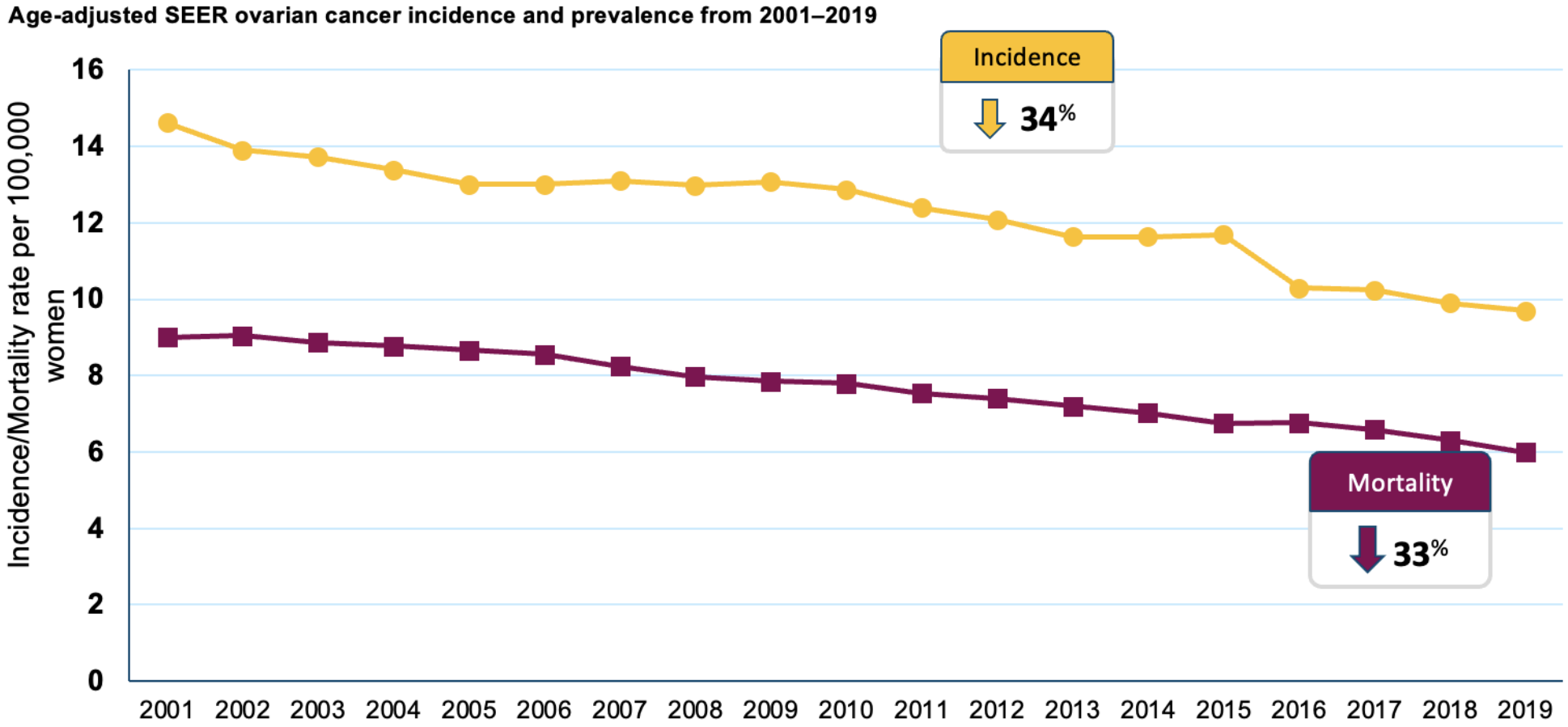
8th most common cause of cancer-related deaths in women globally[2]

In Europe, an estimated **66,693** people were diagnosed with ovarian cancer in 2020[2]

>50% of patients have distant metastases at diagnosis, and **~70%** will die within 5 years[2]

1. Bray F, et al. CA Cancer J Clin 2018;68:394–424; 2. Sung H, et al. CA Cancer J Clin 2021;71:209-249; 3. https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=population&mode_population=continents&population=900&populations=900&key=asr&sex=2&cancer=25&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=0&include_nmsc_other=1 (Accessed August 2022).
2. GLOBOCAN 2018, cancer incidence and mortality produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions.

OVERALL CLINICAL IMPACT OF PARP INHIBITORS IN OVARIAN CANCER



SEER=Surveillance, Epidemiology and End Results.

National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER). SEER Cancer Statistics Review (CSR) 1975-2019 - Ovary. 2019; https://seer.cancer.gov/statistics-network/explorer/application.html?site=61&data_type=5&graph_type=11&compareBy=age_range&chk_age_range_1=1&chk_age_range_9=9&chk_age_range_141=141&chk_age_range_157=157&series=9&hdn_sex=3&advopt_compprev_y_axis_var=0&hdn_view=1#tableWrap; Accessed Aug 14, 2022.

Courtesy of R. Coleman

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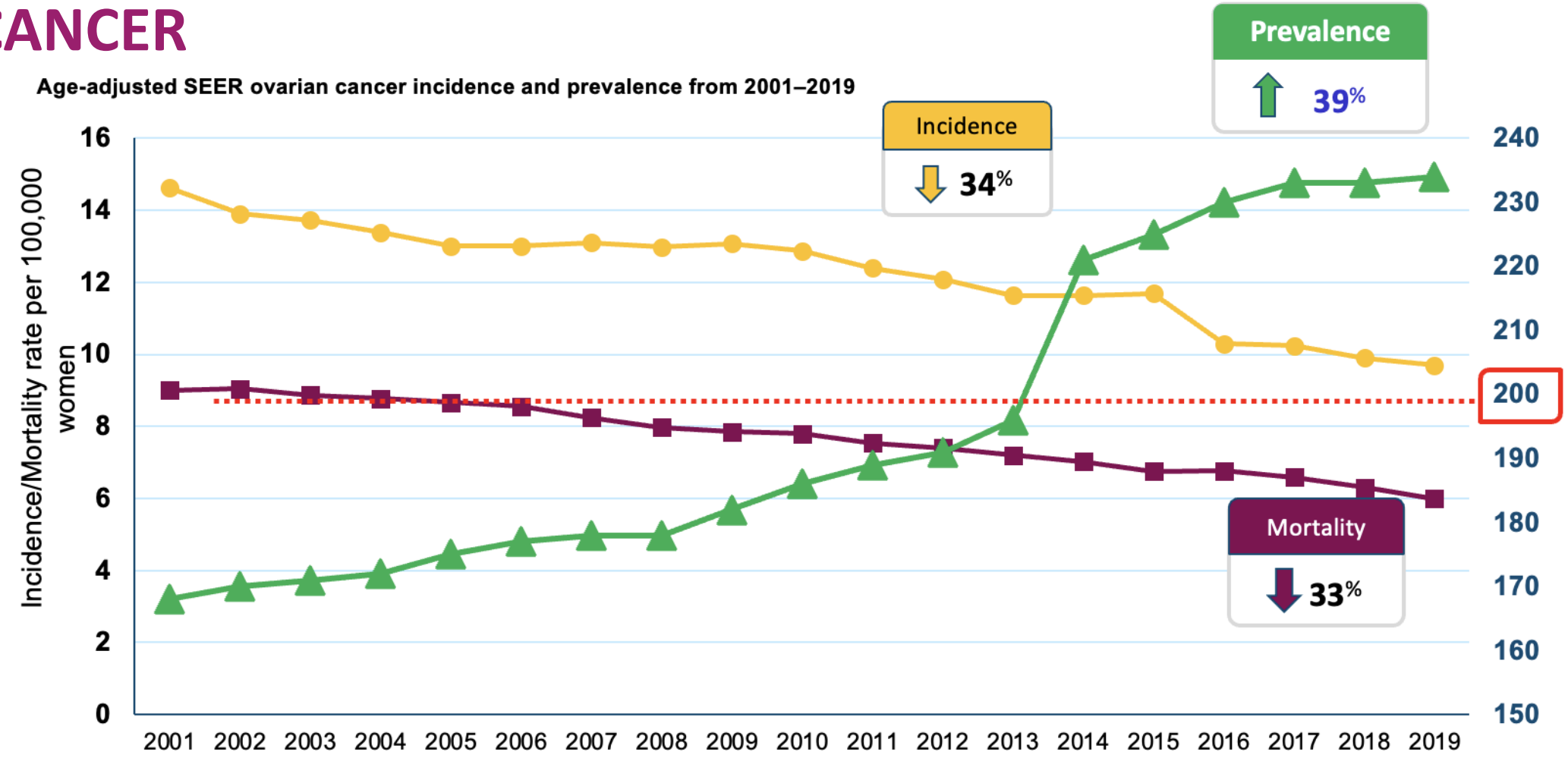


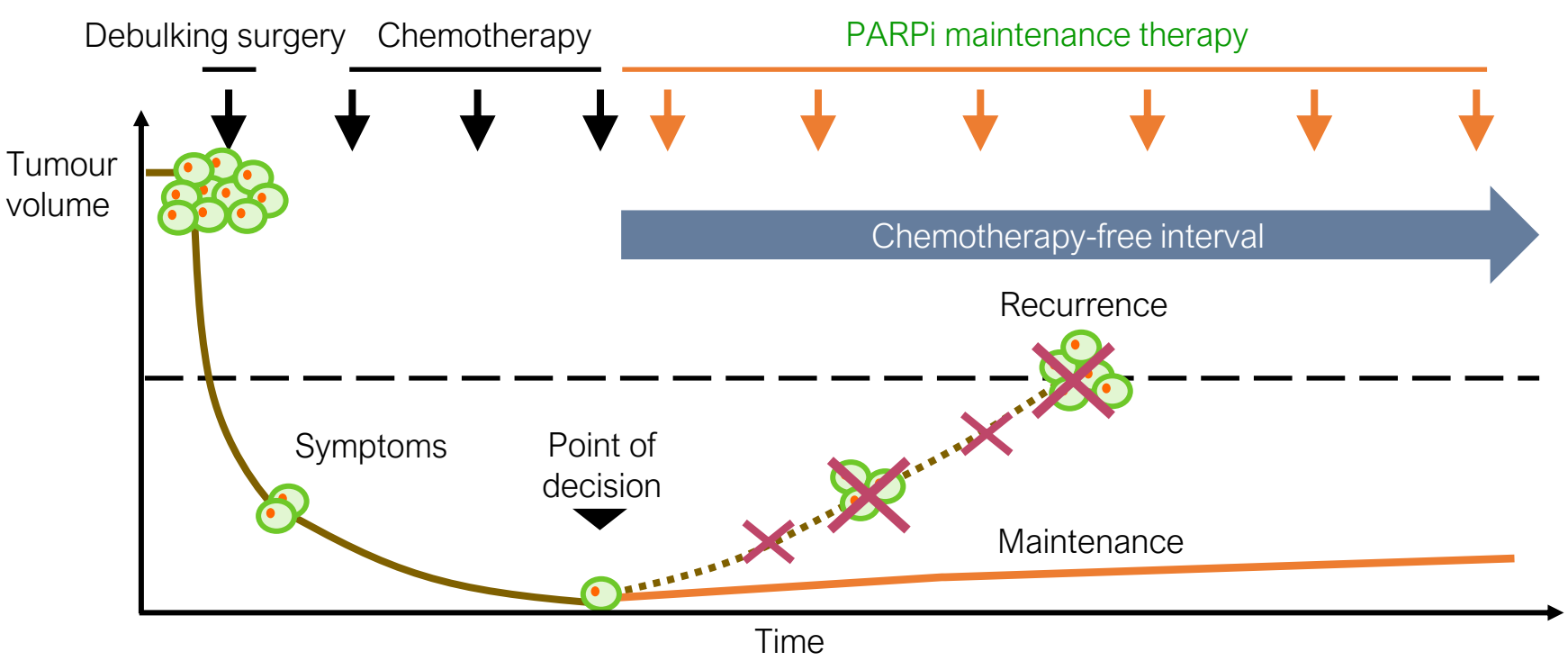
SEER=Surveillance, Epidemiology and End Results.

National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER). SEER Cancer Statistics Review (CSR) 1975-2019 - Ovary. 2019; https://seer.cancer.gov/statistics-network/explorer/application.html?site=61&data_type=5&graph_type=11&compareBy=age_range&chk_age_range_1=1&chk_age_range_9=9&chk_age_range_141=141&chk_age_range_157=157&series=9&hdn_sex=3&advopt_compprev_y_axis_var=0&hdn_view=1#tableWrap; Accessed Aug 14, 2022.

Courtesy of R. Coleman

The ovarian cancer challenge: excellent response to chemotherapy, frequent recurrences

Management of OC:[1]



Goals of maintenance therapy

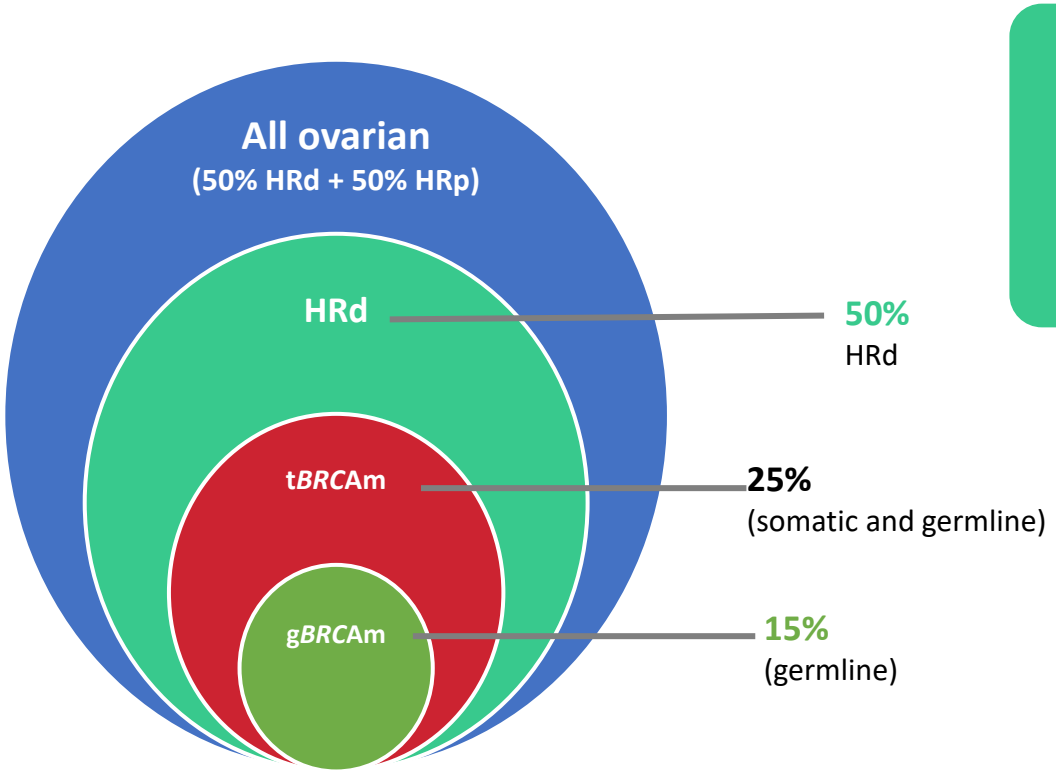
1. Prolong benefit following surgery and chemotherapy
2. Improve survival (PFS and hopefully OS)
3. Manageable toxicity and no negative effects on QoL

>70% of patients with advanced OC will recur within 3–5 years in the absence of 1L maintenance therapy[2,3]

1. DiSilvestro P, Alvarez Secord A. Cancer Treat Rev 2018;69:53-65
2. Ledermann JA, et al. Ann Oncol 2013;24:vi24–vi32
3. du Bois A, et al. Cancer 2009;115:1234–44.

Exploiting Biomarker subgroups in high-grade serous ovarian cancer to optimise treatment

Half of high-grade serous ovarian cancer exhibit a high degree of genomic instability due to deficiencies in homologous recombination



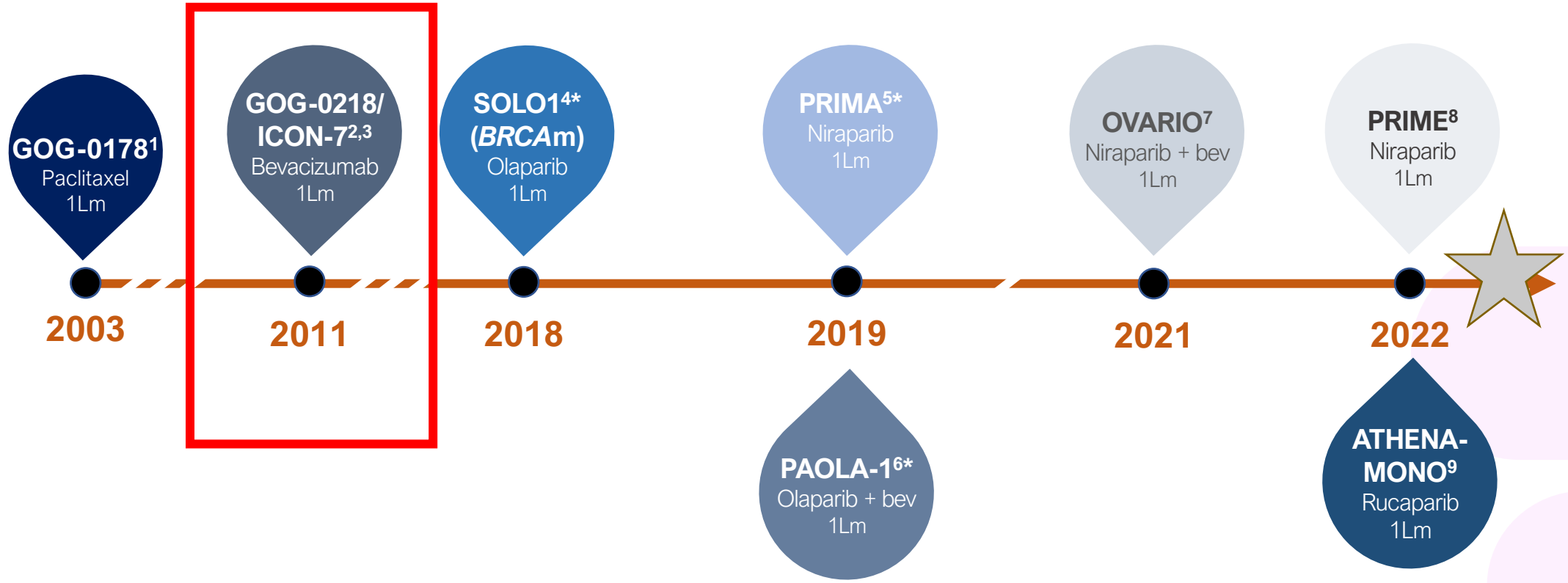
50% are HRd including *BRCA*m, *BRCA*1/2 and RAD51 promoter methylation, BRIP1, and other genes involved in homologous recombination

25% are t*BRCA*m at diagnosis

15% are g*BRCA*m at diagnosis

BRCA, breast cancer gene; BRIP1, *BRCA1*-interacting protein; g*BRCA*, germline BRCA mutant; HR, homologous recombination deficient; OC, ovarian cancer; t*BRCAm*, tumour BRCA mutant.
The Cancer Genome Atlas Research Network, Nature 2011;474:609–15; Konstantinopoulos PA, et al. Cancer Discov 2015;11:1137–54.

Milestones in the evolution of maintenance therapy: reshaping the standard of care for ovarian cancer

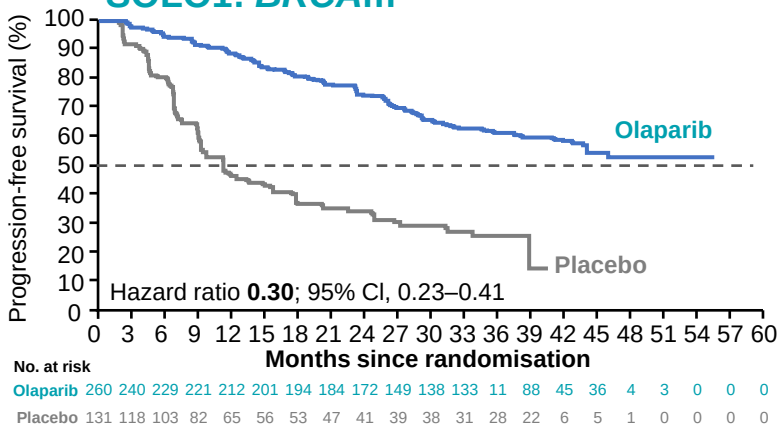


Long-term data readouts for PRIMA, SOLO1 and PAOLA-1 in 2022

1. Markman M, et al. J Clin Oncol 2003;21:2460–5;
2. Burger RA, et al. N Engl J Med 2011;365:2473–83;
3. Perren TJ, et al. N Engl J Med 2011;365:2484–96;
4. Moore K, et al. N Engl J Med 2018;379:2495–505;
5. González-Martín A, et al. N Engl J Med 2019;381:2391–402;
6. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–28;
7. Hardesty MM, et al. Gynecol Oncol 2022;166:219-29;
8. Li N, et al. presented at SGO 2022, 18–21 Mar, Phoenix, AZ;
9. Monk BJ, et al. J Clin Oncol 2022; https://doi.org/10.1200/JCO.22.01003.

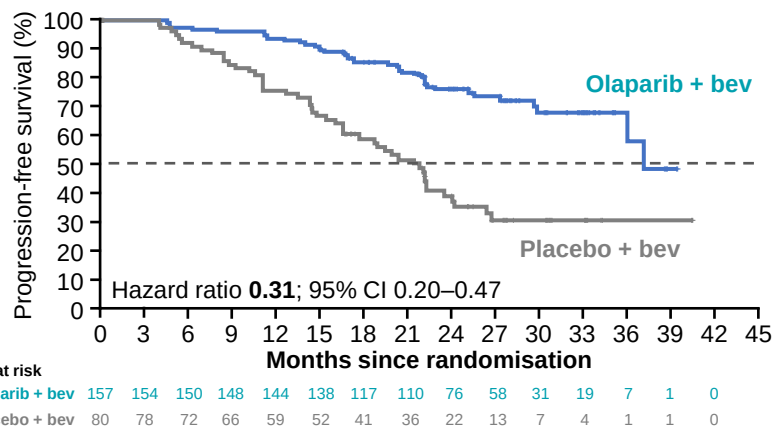
Consistent PFS benefit with PARPi maintenance therapy in patients with *BRCA*m tumours

SOLO1: *BRCA*m[1]



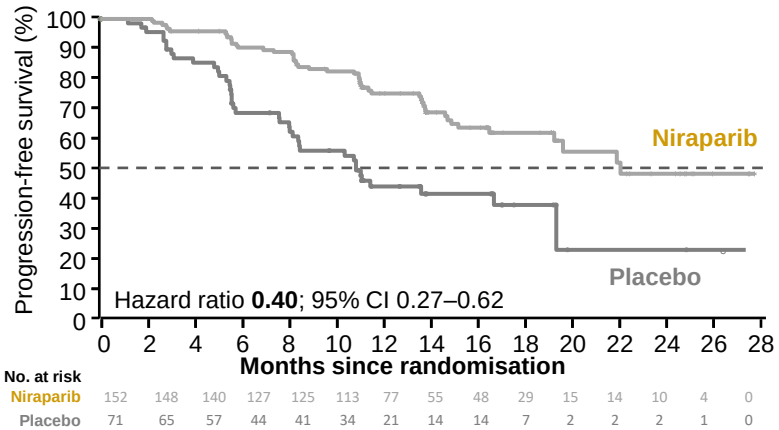
No. at risk																			
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	11	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

PAOLA-1: *BRCA*m[2]



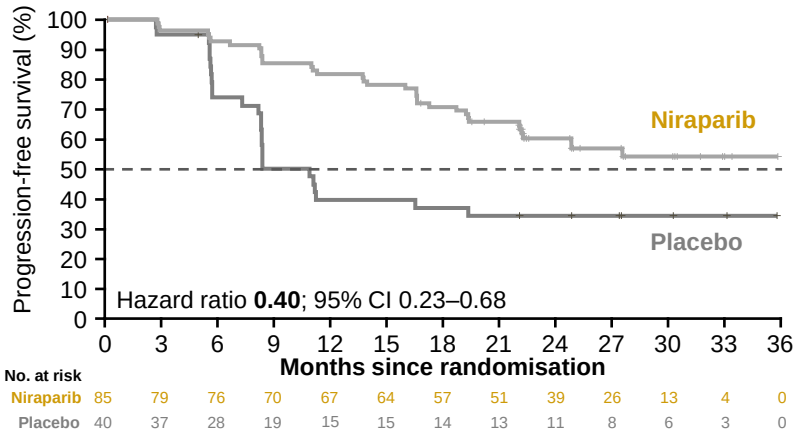
No. at risk															
Olaparib + bev	157	154	150	148	144	138	117	110	76	58	31	19	7	1	0
Placebo + bev	80	78	72	66	59	52	41	36	22	13	7	4	1	1	0

PRIMA: *BRCA*m[3]



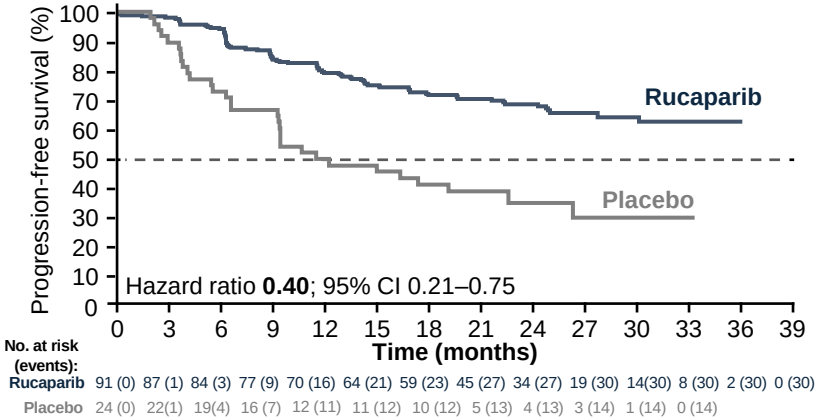
No. at risk															
Niraparib	152	148	140	127	125	113	77	55	48	29	15	14	10	4	0
Placebo	71	65	57	44	41	34	21	14	14	7	2	2	2	1	0

PRIME: *BRCA*m[4]



No. at risk													
Niraparib	85	79	76	70	67	64	57	51	39	26	13	4	0
Placebo	40	37	28	19	15	15	14	13	11	8	6	3	0

ATHENA-MONO: *BRCA*m[5]



No. at risk (events):														
Rucaparib	91 (0)	87 (1)	84 (3)	77 (9)	70 (16)	64 (21)	59 (23)	45 (27)	34 (27)	19 (30)	14(30)	8 (30)	2 (30)	0 (30)
Placebo	24 (0)	22(1)	19(4)	16 (7)	12 (11)	11 (12)	10 (12)	5 (13)	4 (13)	3 (14)	1 (14)	0 (14)		

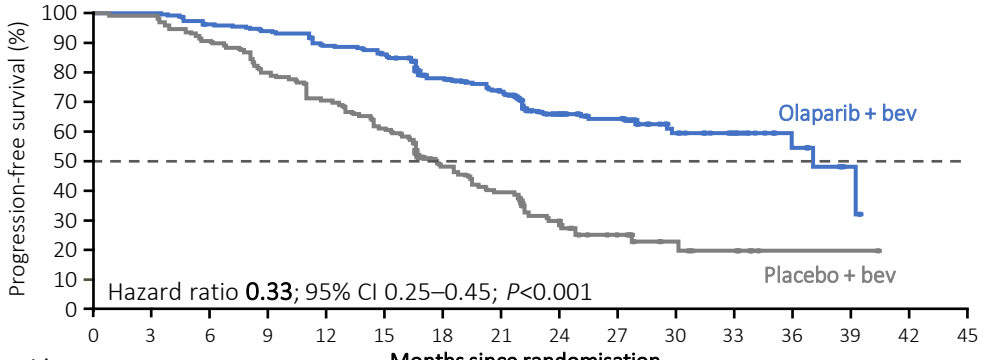
There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting data.
These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

PRIME was sponsored by Zai Lab (Shanghai) Co., Ltd. Bev, bevacizumab; *BRCA*m, breast cancer gene mutant; CI, confidence interval; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival.

1. Moore K, Colombo N, Scambia G, et al. N Engl J Med. 2018 Dec 27;379(26):2495-2505. 2. Ray-Coquard I, Pautier P, Pignata S, et al; PAOLA-1 Investigators. N Engl J Med. 2019 Dec 19;381(25):2416-28. 3. Figure from González-Martín A, Pothuri B, Vergote I, et al. Niraparib therapy in patients with newly diagnosed advanced ovarian cancer (PRIMA/ENGOT-OV26/GOG-3012). Presented at ESMO 2019. 27th September- 1st October, Barcelona, Spain. 4. Li N, Zhu J, Yin R, et al. JAMA Oncol. 2023 Sep 1;9(9 Suppl):1230-7. 5. Monk BJ, Parkinson C, Lim MC, et al. J Clin Oncol. 2022 Dec 1;40(34):3952-3964.

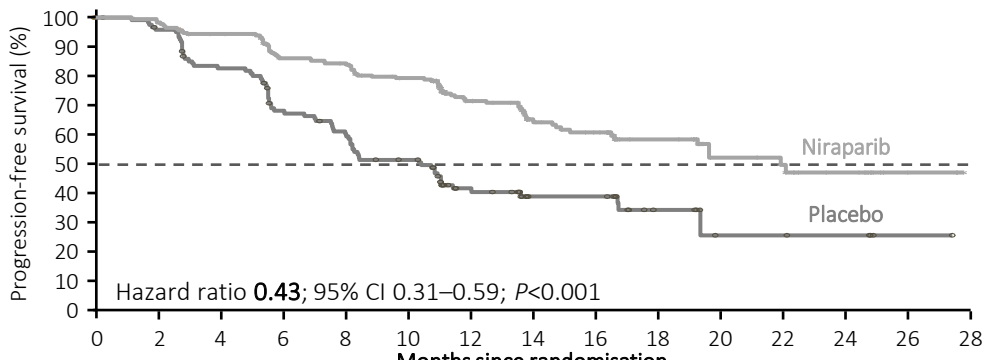
Consistent PFS benefit with PARPi maintenance therapy in patients with HRd tumours

PAOLA-1: HRd[1]



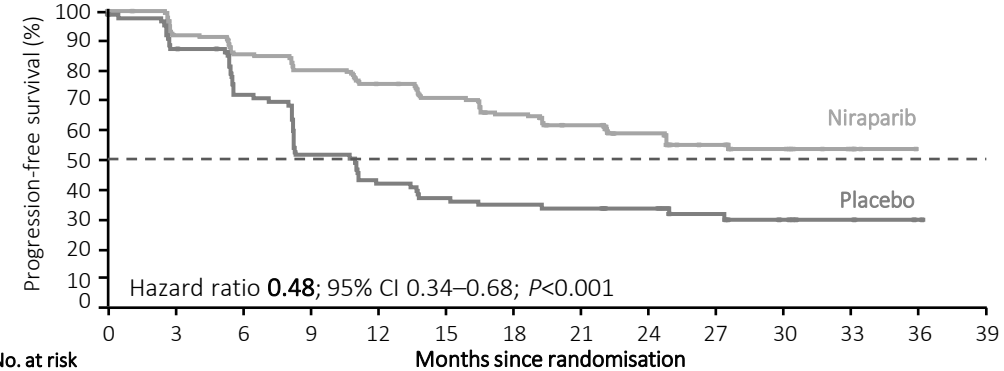
No. at risk															
Olaparib + bev	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo + bev	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

PRIMA: HRd[3]



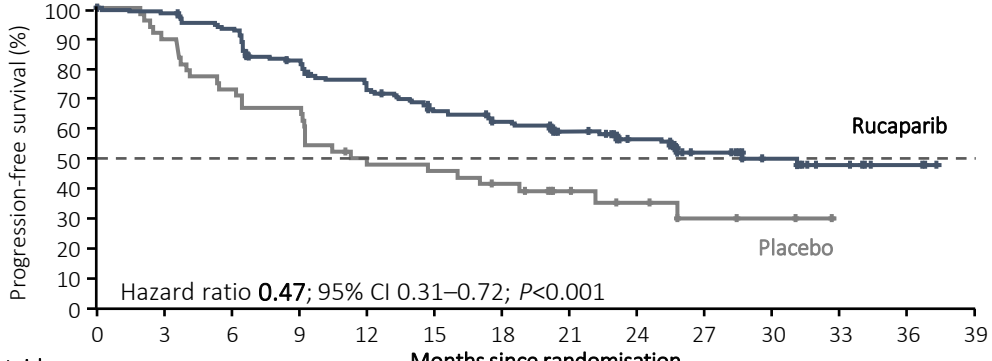
No. at risk															
Niraparib	247	231	215	189	184	168	111	76	66	42	22	19	13	4	0
Placebo	126	117	99	79	70	57	34	21	21	11	5	5	4	1	0

PRIME: HRd[2]



No. at risk														
Niraparib	170	150	139	130	121	112	102	93	75	51	26	10	0	0
Placebo	87	76	60	43	35	31	29	28	24	16	12	4	1	0

ATHENA-MONO: HRd[4]



No. at risk														
Rucaparib	185	175	165	143	127	110	100	82	59	36	22	12	3	0
Placebo	49	43	35	32	22	21	18	11	8	4	2	0		

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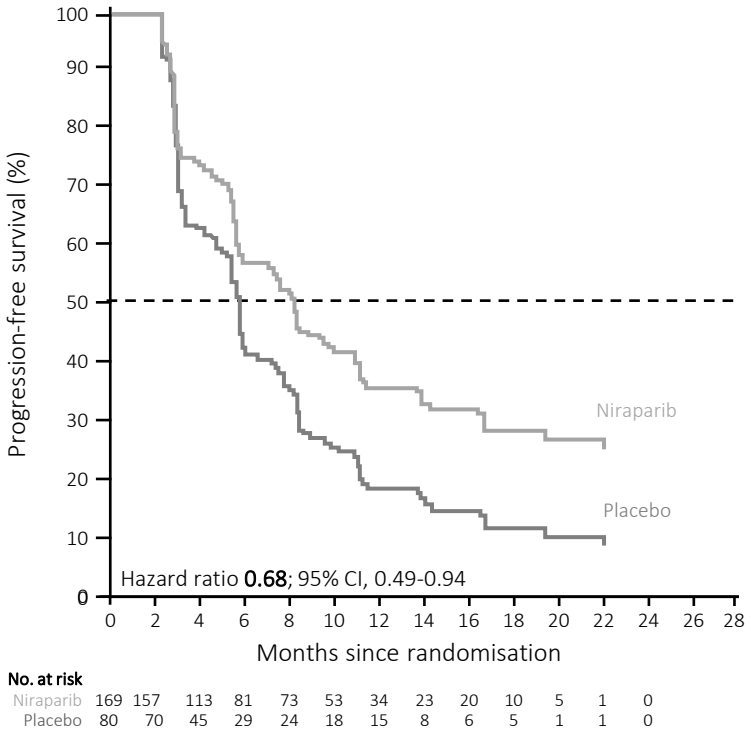
1. Figure adapted from N Engl J Med, Ray-Coquard et al, Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer, Volume 381, Pages 2416–28. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. 2. Li N, Zhu J, Yin R, et al. JAMA Oncol. 2023 Sep 1;9(9 Suppl):1230-7. 3. Figure from N Engl J Med, González-Martín et al, Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume 381, Pages 2391–402. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. 4. Monk BJ, Parkinson C, Lim MC, et al. J Clin Oncol. 2022 Dec 1;40(34):3952-64.

PFS benefit in HRp observed only with PARPi monotherapy

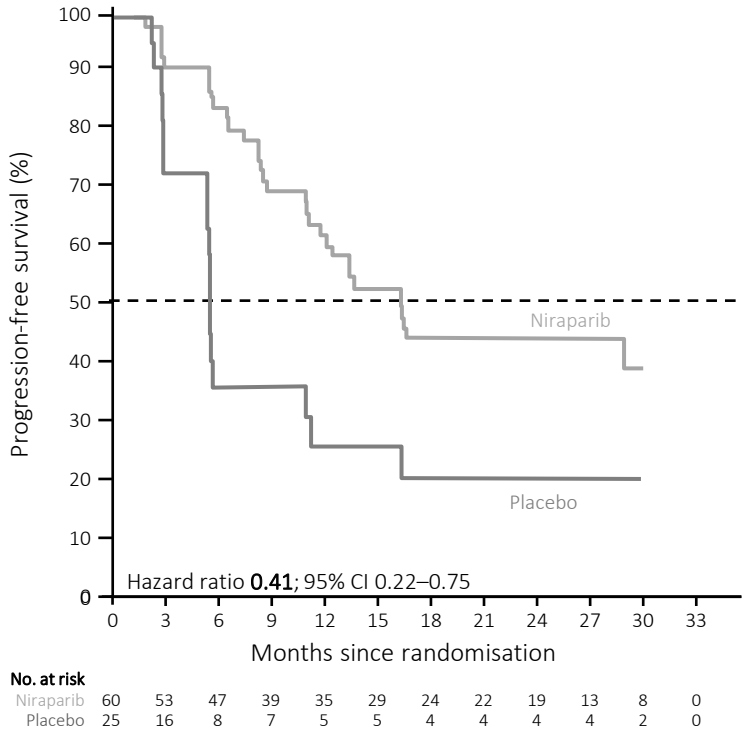
PRIMA: HRp[1]



No. at risk

Niraparib	169	157	113	81	73	53	34	23	20	10	5	1	0
Placebo	80	70	45	29	24	18	15	8	6	5	1	1	0

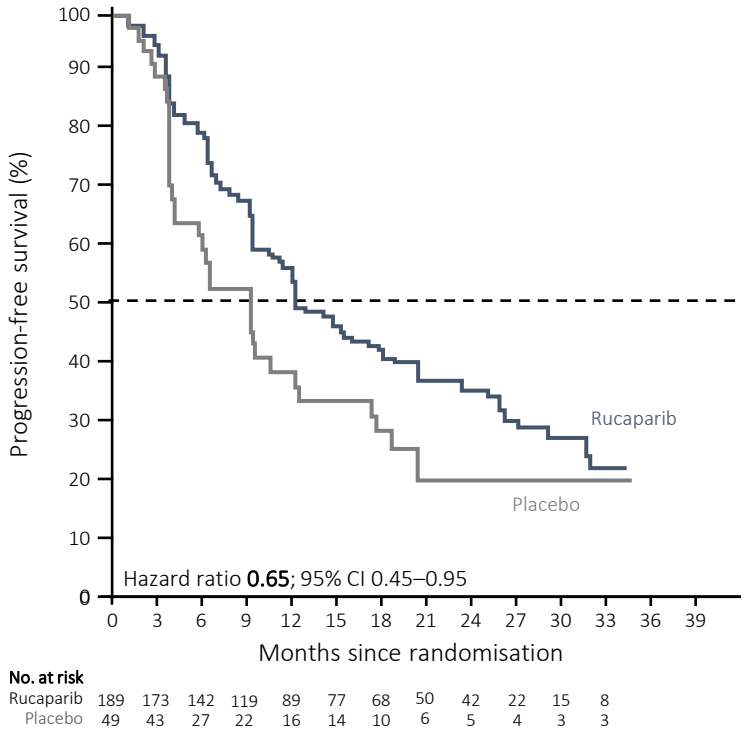
PRIME: HRp[2]



No. at risk

Niraparib	60	53	47	39	35	29	24	22	19	13	8	0
Placebo	25	16	8	7	5	5	4	4	4	4	2	0

ATHENA-MONO: HRp[3]



No. at risk

Rucaparib	189	173	142	119	89	77	68	50	42	22	15	8
Placebo	49	43	27	22	16	14	10	6	5	4	3	3

There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

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CI, confidence interval; HRp, homologous recombination proficient; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival.
1. González-Martín A, Pothuri B, Vergote I, et al. Niraparib therapy in patients with newly diagnosed advanced ovarian cancer (PRIMA/ENGOT-OV26/GOG-3012). Presented at ESMO 2019. 27th September- 1st October, Barcelona, Spain.
2. Li N, Zhu J, Yin R, et al. JAMA Oncol. 2023 Sep 1;9(9 Suppl):1230-7. 3. Monk BJ, Parkinson C, Lim MC, et al. *J Clin Oncol*. 2022 Dec 1;40(34):3952-64.

11

Real-world data also confirm that PARPi maintenance monotherapy extends progression-free survival vs active surveillance

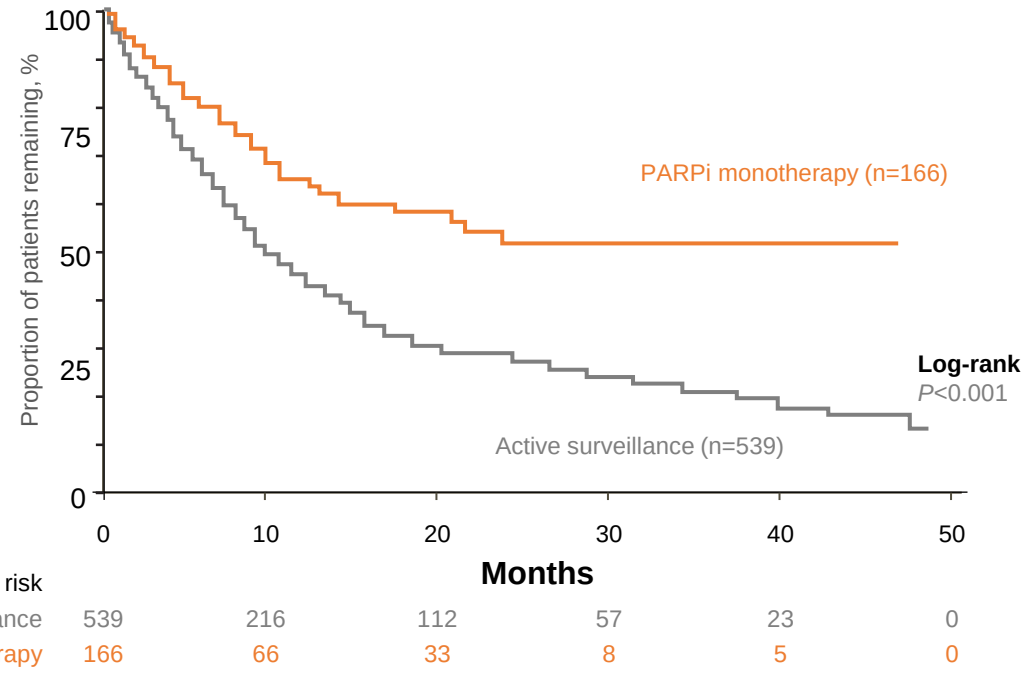
Longer rwPFS with PARPi monotherapy vs active surveillance

time to event, median (95%)

PARPi monotherapy (n=166)	**NR** (19.5-NR)	***P*<0.001**
Active surveillance (n=539)	**9.5 months** (8.4-11.2)	

Median follow-up was 10.9 months for PARPi monotherapy and 20.6 months for AS

Real-world PFS in overall population
(N=705)



Patients at risk						
Active surveillance	539	216	112	57	23	0
PARPi monotherapy	166	66	33	8	5	0

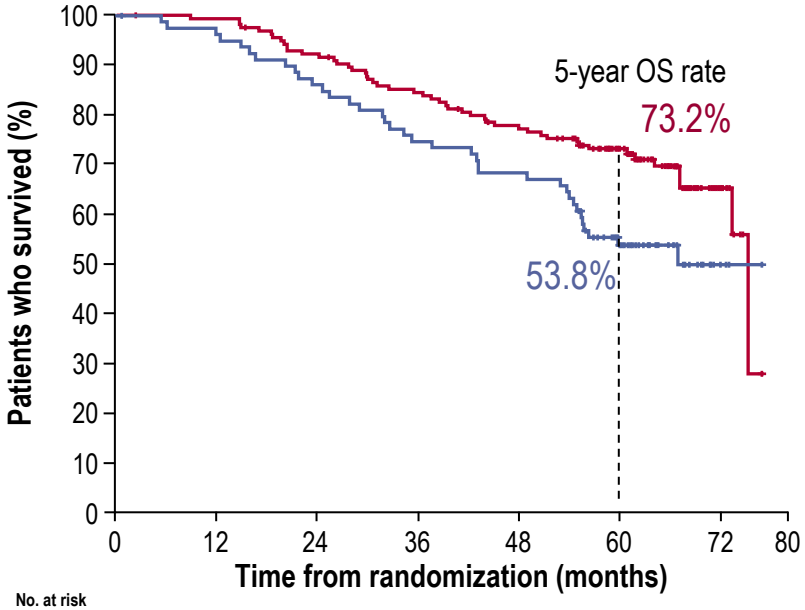
- Patients diagnosed with advanced ovarian cancer from a national database who, after completing 1L platinum-based chemotherapy (PBCT), either received PARPi monotherapy or underwent active surveillance (AS)
- PARPi cohort received first dose after the last dose of PBCT; AS cohort did not receive 1L maintenance therapies after last dose of PBCT and before any 2L therapy

1L, first line; 2L, second line; NR, not reached; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival; rwPFS, real-world progression free survival.

1. Chan JK, Liu J, Song J, et al. Am J Clin Oncol. 2023 Jul 1;46(7):314-22.

OS subgroup analysis by BRCAm and HRD status

BRCAm*

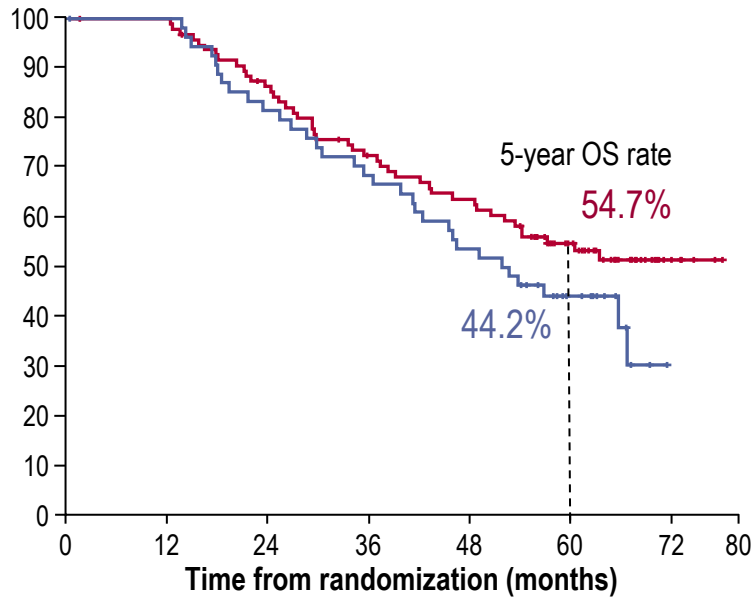


No. at risk

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

	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)	

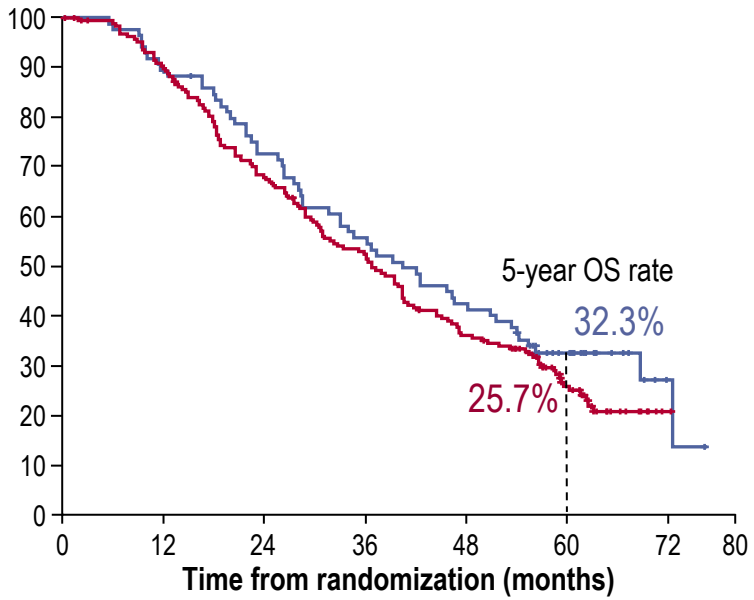
HRD positive‡ excluding BRCAm



Olaparib + bevacizumab	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
Placebo + bevacizumab	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†



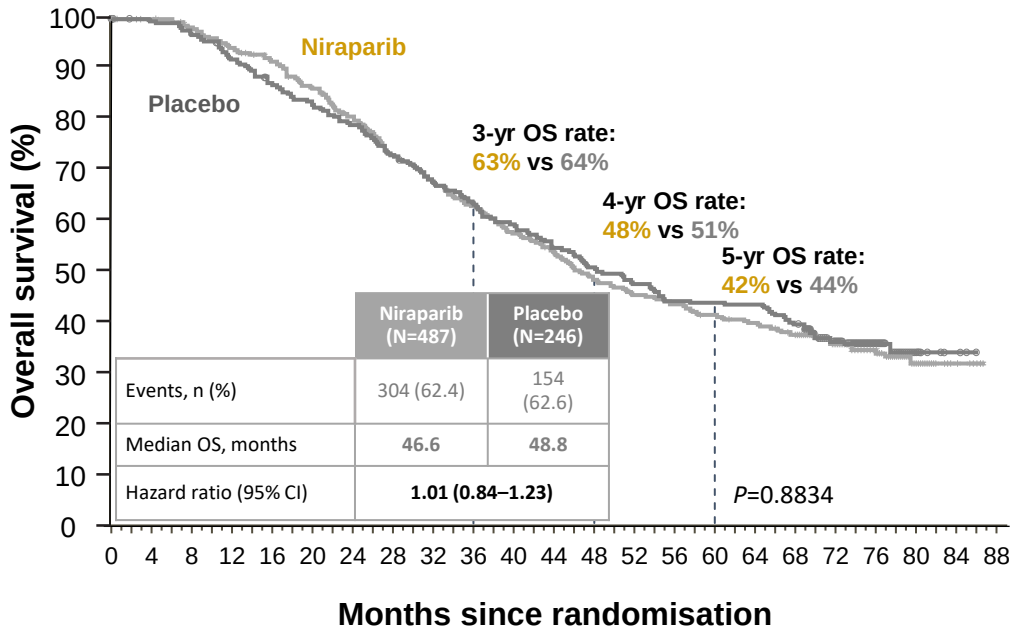
Olaparib + bevacizumab	192	187	186	179	169	157	146	135	126	119	109	100	97	89	77	72	66	62	57	43	30	16	11	5	1	0	
Placebo + bevacizumab	85	85	84	83	76	74	71	65	60	56	51	48	46	43	41	38	35	33	31	21	17	11	8	5	2	1	0

	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.

Final OS analysis showed no difference between treatment arms in the ITT and HRd populations

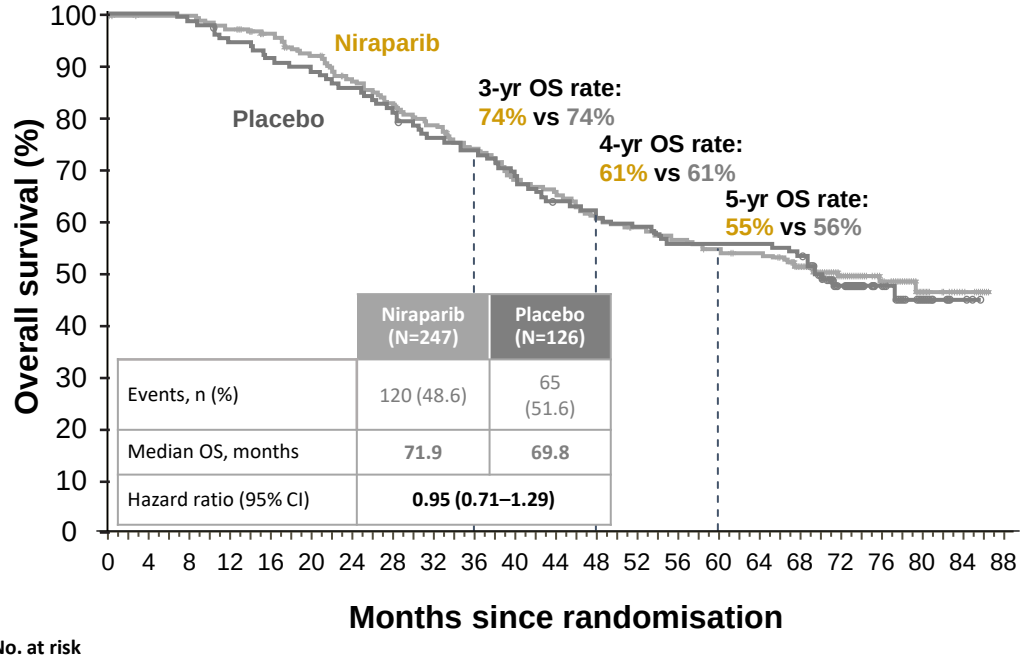
OS in ITT Population



No at risk

Niraparib	487	482	470	451	432	406	378	343	318	294	268	250	227	211	202	192	183	170	115	57	23	5	0		
Placebo	246	243	230	223	210	201	191	177	163	153	143	131	121	114	106	105	104	95	62	26	11	3			

OS in HRd Population



No. at risk

Niraparib	247	245	244	236	231	220	207	196	186	173	159	154	143	137	131	126	123	115	75	43	19	5	0		
Placebo	126	126	124	115	114	111	107	102	94	91	86	78	75	72	68	68	68	65	40	20	10	3			

- At the data cutoff of 8 April 2024, median follow-up duration was **6.2 years** with 62.5% OS data maturity in the **ITT** population and with **49.6%** in the **HRd** population
- In the niraparib group, **median OS** was **~47 months** for **ITT** population and ~**72 months** for **HRd population despite high-risk patient characteristics**

Data are ad hoc, investigator-assessed OS. Based on the hierarchical testing in the statistical analysis plan, OS in HRd population and beyond cannot be evaluated for statistical significance when *P*≥0.025 in the ITT population.
HRd, homologous recombination deficient; ITT, intention to treat; OS, overall survival; yr, year.
1. Monk BJ, Barretina-Ginesta MP, Pothuri B, et al. Ann Oncol. September 2024.

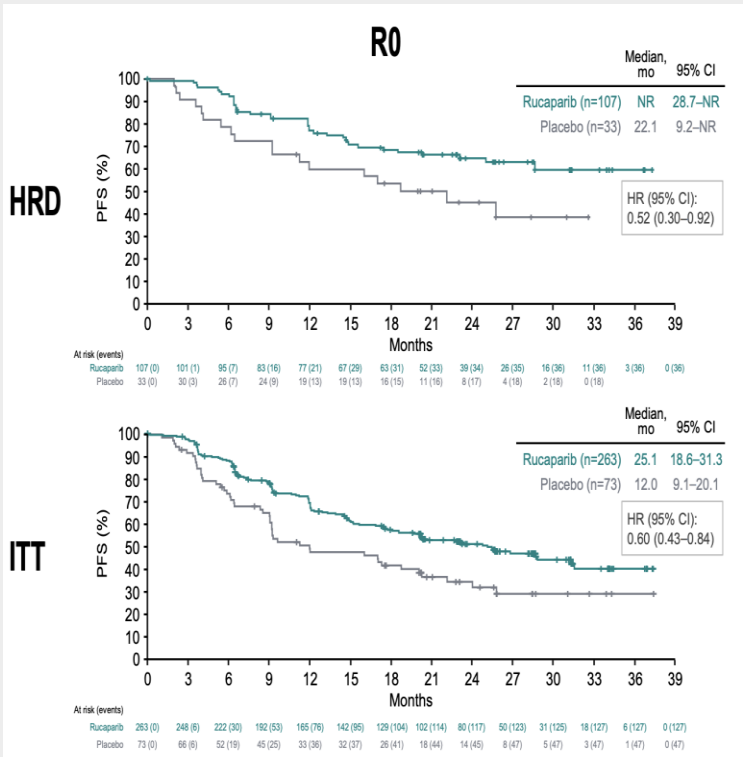
Subsequent PARPi?

Trial	Placebo	PARPi
SOLO1	44.3	14.6
PAOLA	45.7	19.6
PRIMA	37.8 BRCA+: 57.7	11.7 BRCA+: 19.1
ATHENA	not reported	Not reported

There might be an imbalance, but could a difference of <15% explain the results?

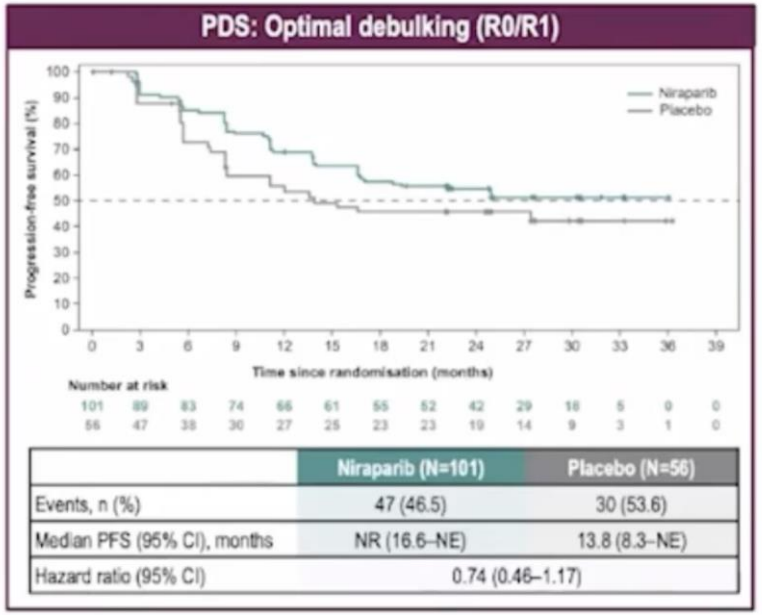
The benefit of PARP seems to be higher in RT=0 patients

ATHENA



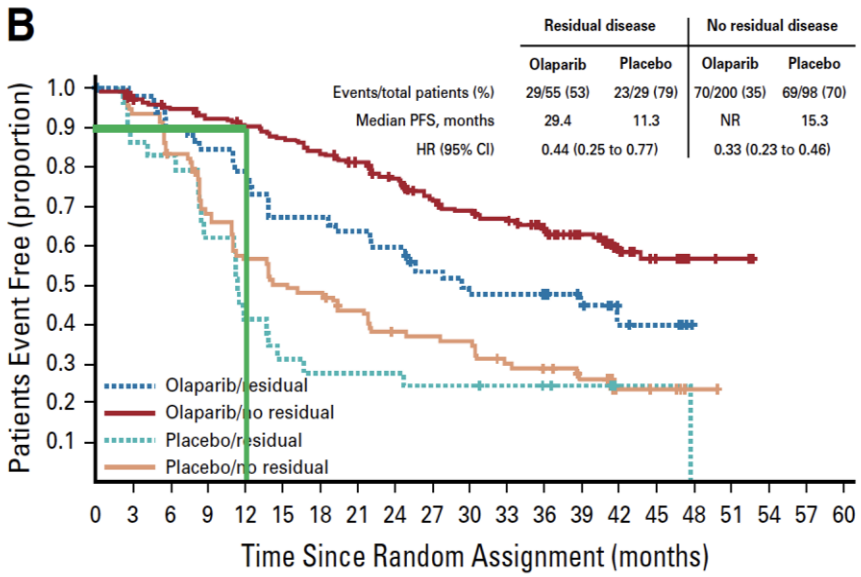
Kristeleit ESMO 2022

PRIME



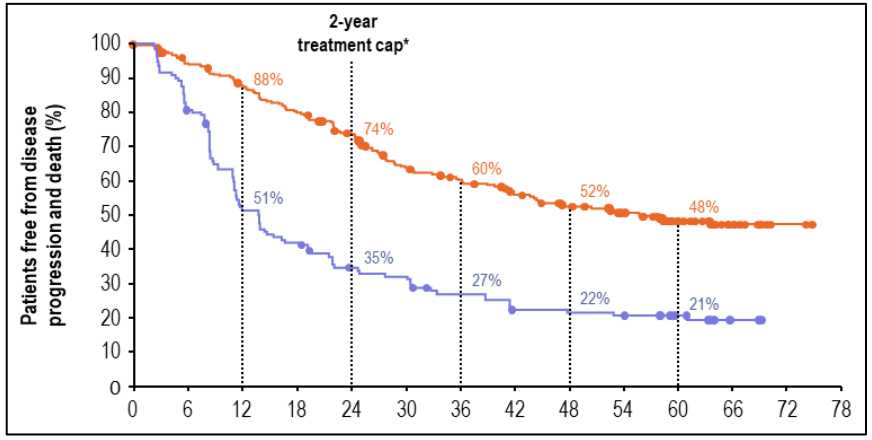
Lingya ESMO gyn 2023

SOLO 1

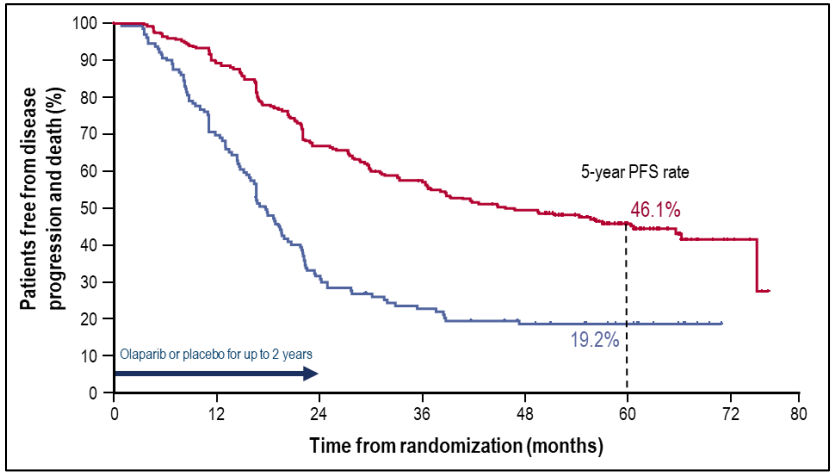


DiSilvestro, JCO 2020

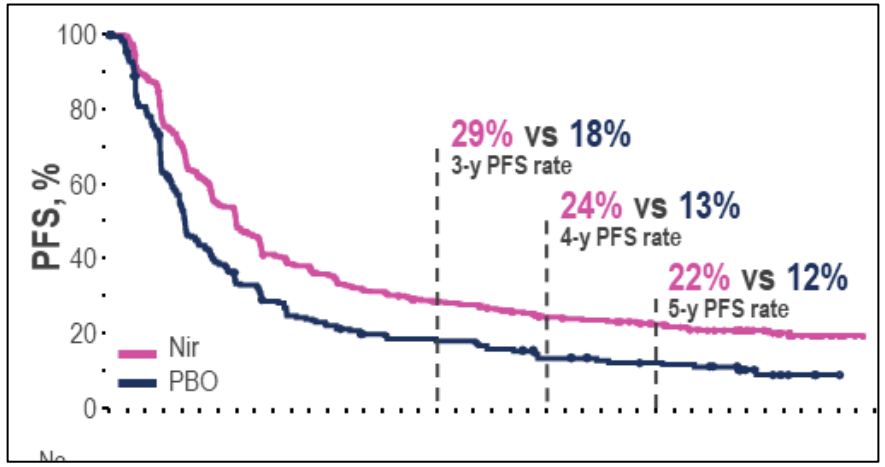
Duration of PARPi and timepoint of relapse



SOLO1: 26% PD during maintenance (2 years)



PAOLA1: ~35% PD during maintenance (2 years)

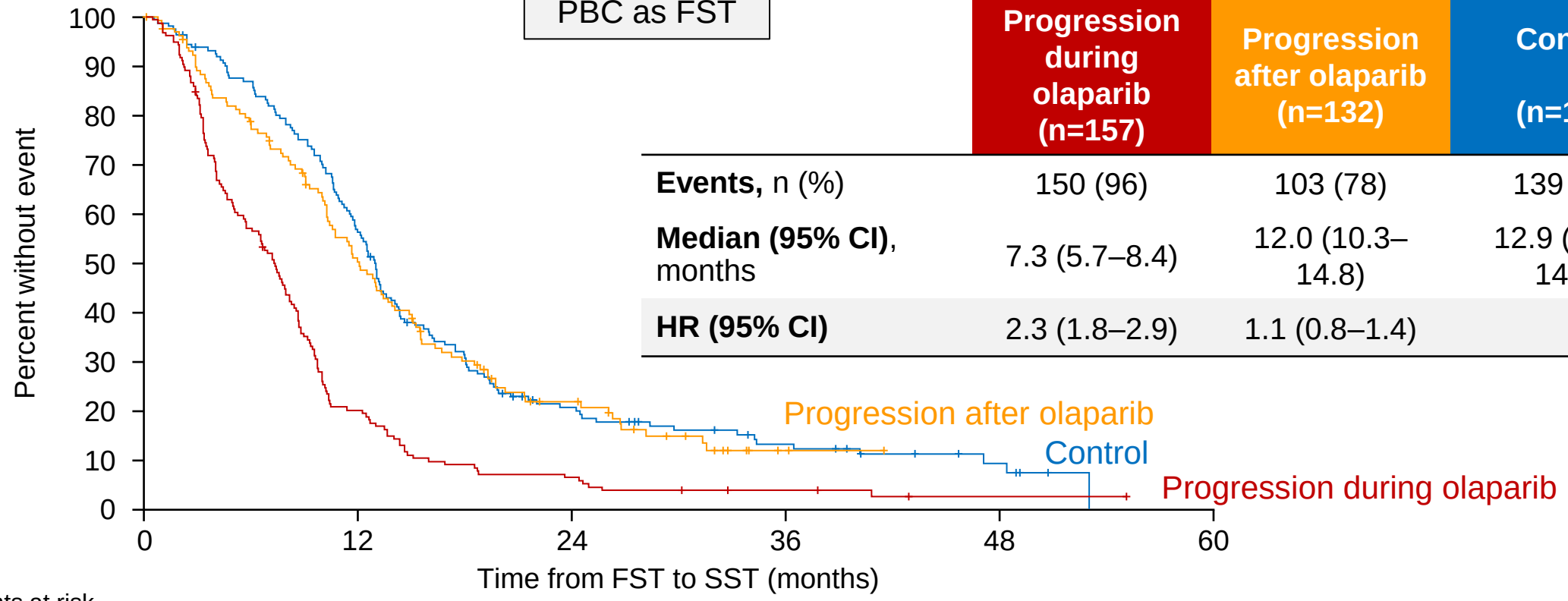


PRIMA: ~ all patients with PD during maintenance (reflecting the included high-risk population + treatment until PD)

For patients receiving PBC as FST, time from FST to SST was shortest in patients who progressed during initial olaparib maintenance

Analysis of time from FST to SST depending on treatment arm and time of relapse

PBC as FST



	Progression during olaparib (n=157)	Progression after olaparib (n=132)	Control (n=162)
Events, n (%)	150 (96)	103 (78)	139 (86)
Median (95% CI), months	7.3 (5.7–8.4)	12.0 (10.3–14.8)	12.9 (11.8–14.1)
HR (95% CI)	2.3 (1.8–2.9)	1.1 (0.8–1.4)	

Patients at risk

Progression after olaparib	132	113	97	83	60	46	35	25	21	14	11	5	2	1	0				
Progression during olaparib	157	130	88	54	31	17	14	11	10	6	6	4	4	3	2	1	1	1	1
Control	162	150	139	120	90	58	45	33	28	24	19	18	14	12	9	8	5	1	0

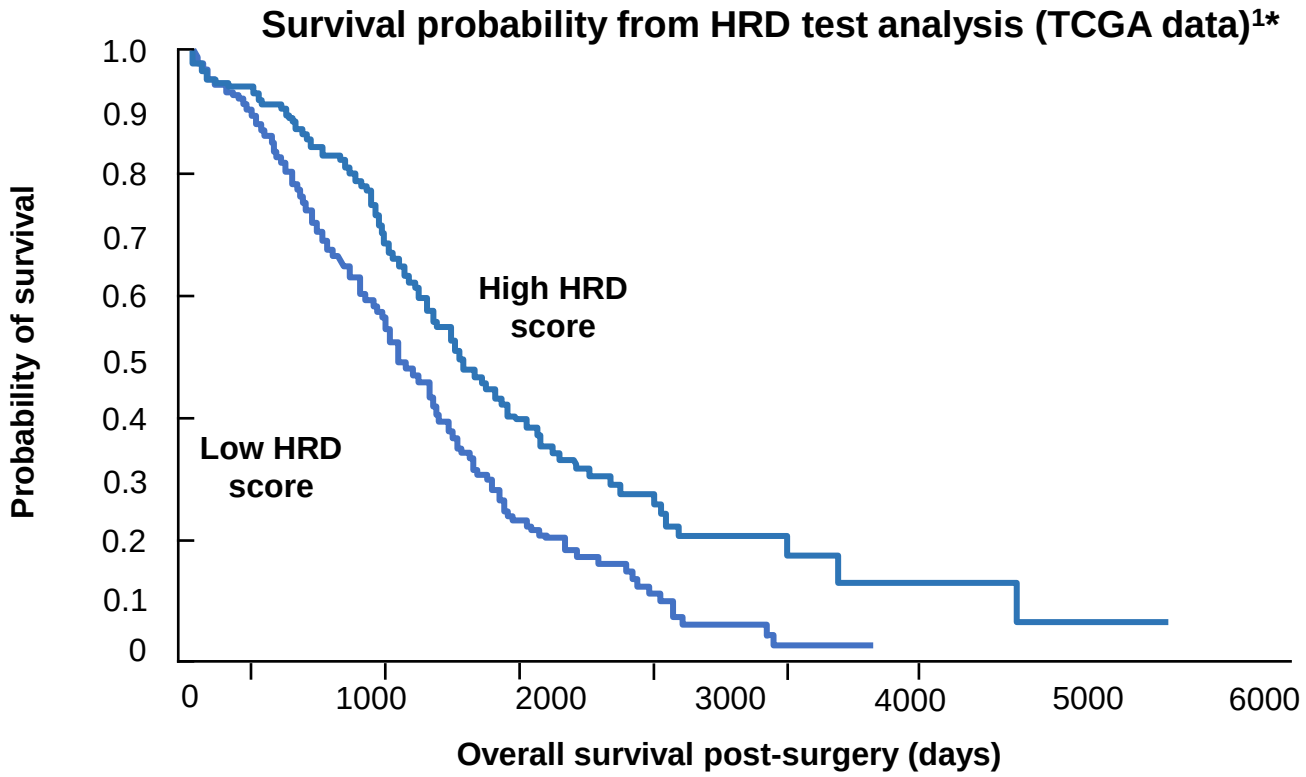
One patient in the olaparib arm did not receive study treatment and is not included in this analysis.

Marth C, et al. ESGO 2023

HRD testing prior to treatment decision-making is recommended by clinical guidelines

HRD tests have a prognostic and predictive role in OC[1-5]

- **Higher HRD** scores are associated with **improved survival**[1]
- In the 1Lm setting, HRD status **is a predictor of benefit** from treatment with **PARPi monotherapy** and combination of **olaparib + bevacizumab**[2-6]

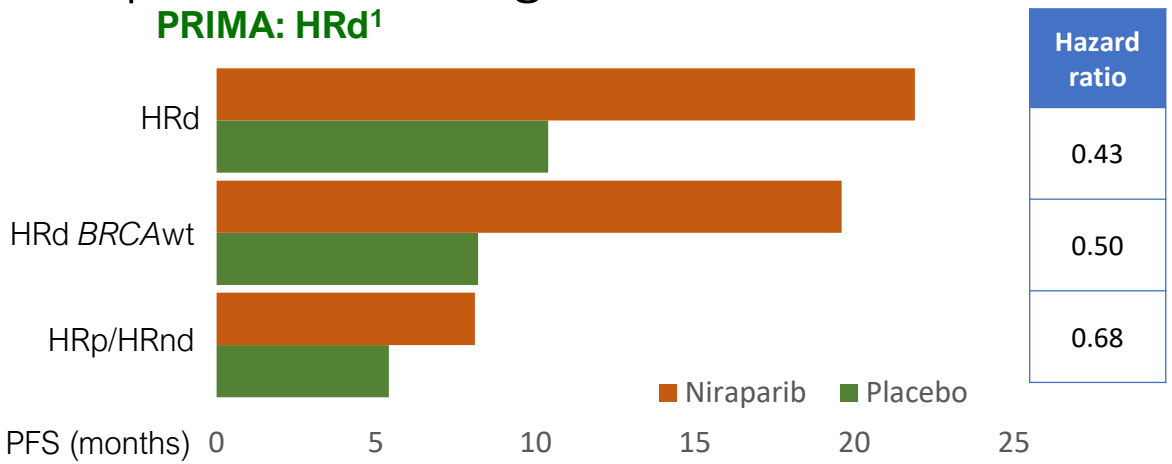


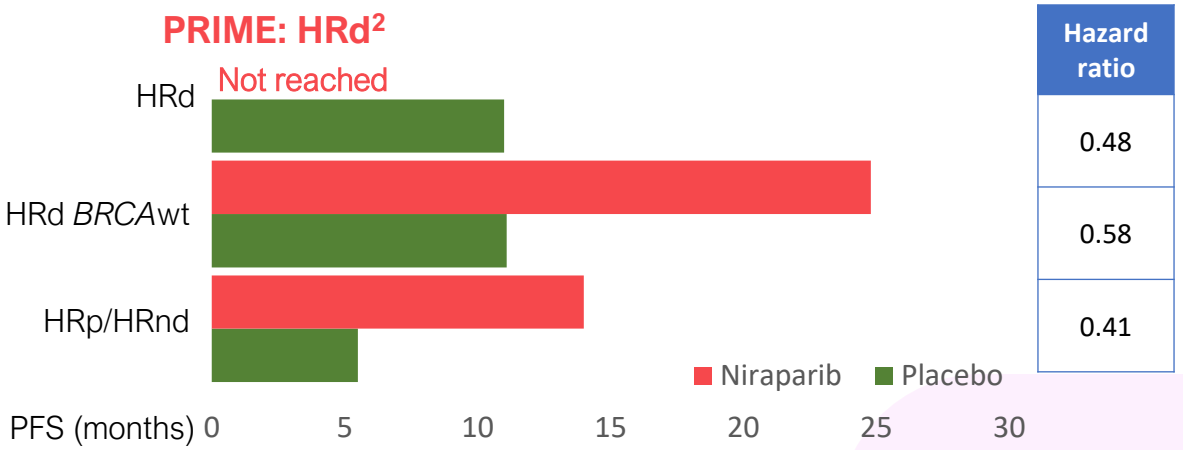
*These data were generated using 507 samples from the TCGA dataset for which copy number data and survival information were available. Median OS for samples with high and low HRd score were 1499 (95% CI: 1355–1769) and 1163 (95% CI: 1081–1354) days, respectively.

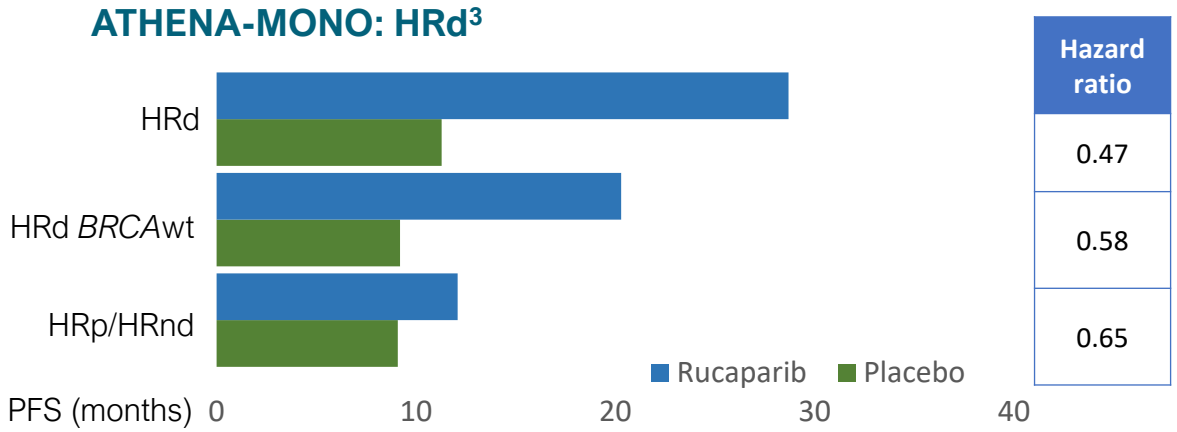
1Lm, first-line maintenance; CI, confidence interval; HRd, homologous recombination deficiency; OC, ovarian cancer; OS, overall survival; PARPi, poly(ADP) ribose polymerase inhibitor; TCGA, The Cancer Genome Atlas Network.

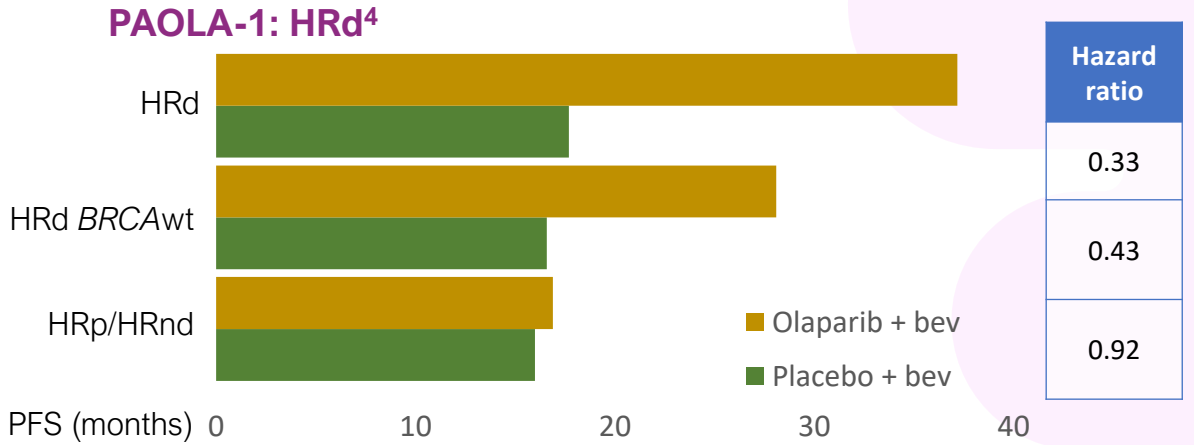
1. Abkevich V, Timms KM, Hennessy BT, et al. Br J Cancer. 2012 Nov 6;107(10):1776-82. 2. Gonzalez-Martin A, Pothuri B, Vergote I, et al. N Engl J Med. 2019 Dec 19;381(25):2391-402. 3 . Li N, Zhu J, Yin R, et al. JAMA Oncol. 2023 Sep 1;9(9):1230-7 4. Monk BJ, Parkinson C, Lim MC, et al. J Clin Oncol. 2022 Dec 1;40(34):3952-64. 5. Ray-Coquard I, Pautier P, Pignata S, N Engl J Med. 2019 Dec 19;381(25):2416-28. 6. González-Martín A, Harter P, Leary A, et al; ESMO Guidelines Committee. Ann Oncol. 2023 Oct;34(10):833-48. 7. Caruso G, Tomao F, Parma G, et al. Int J Gynecol Cancer. 2023 Apr 3;33(4):431-43.

Predictive Value of HR status: in the first line maintenance setting, HRD status clearly predicts for magnitude of PARPi benefit







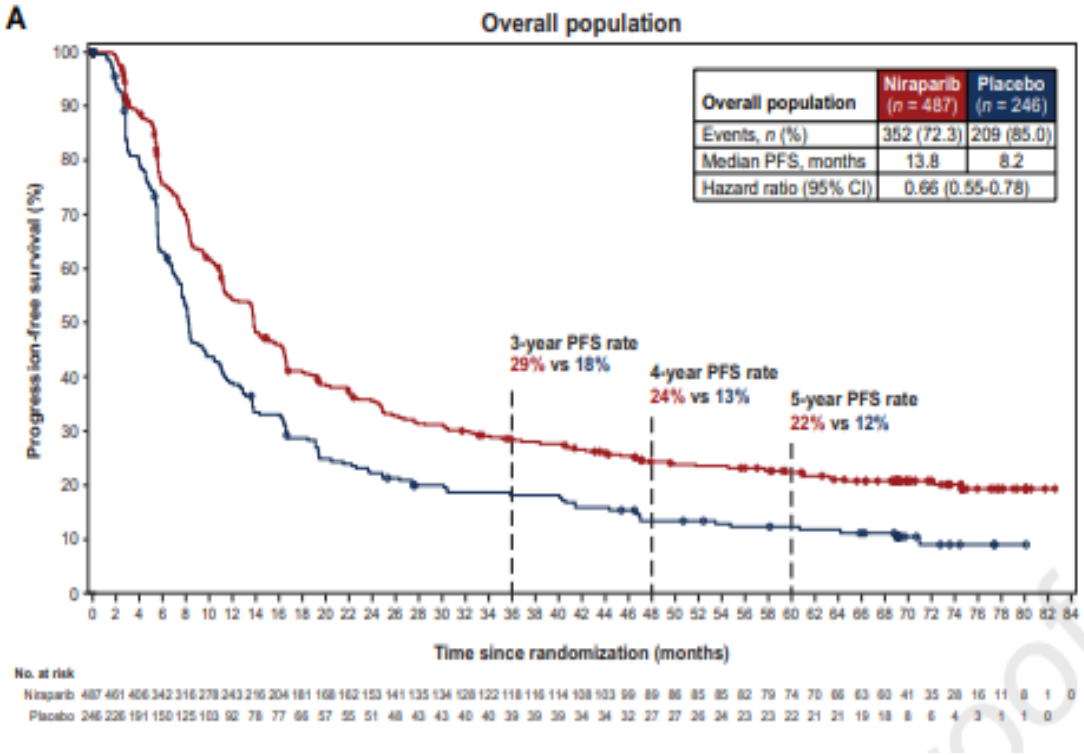


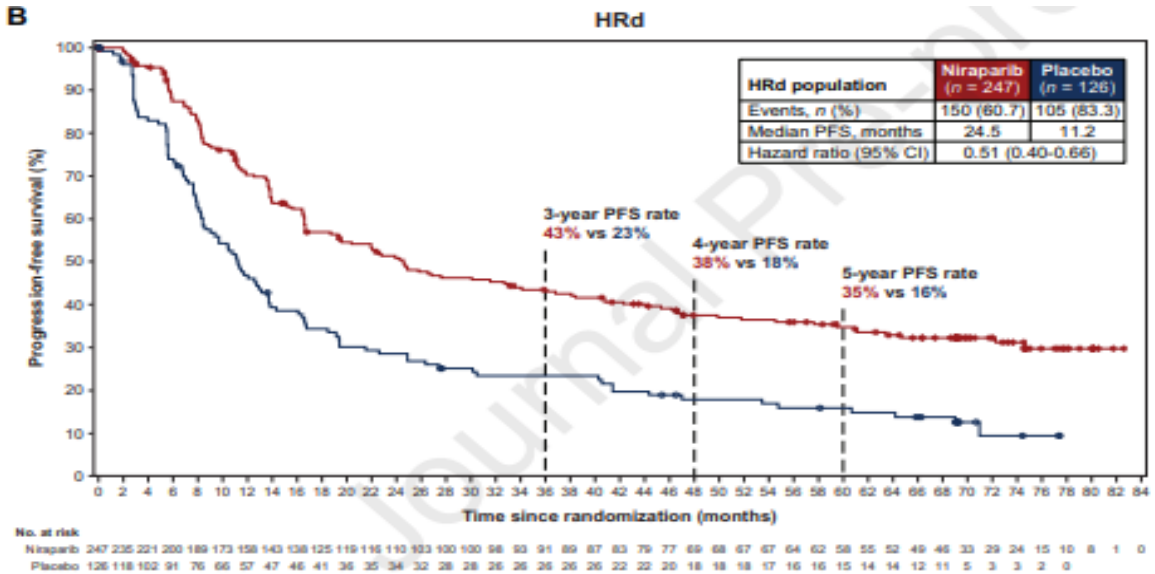
There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

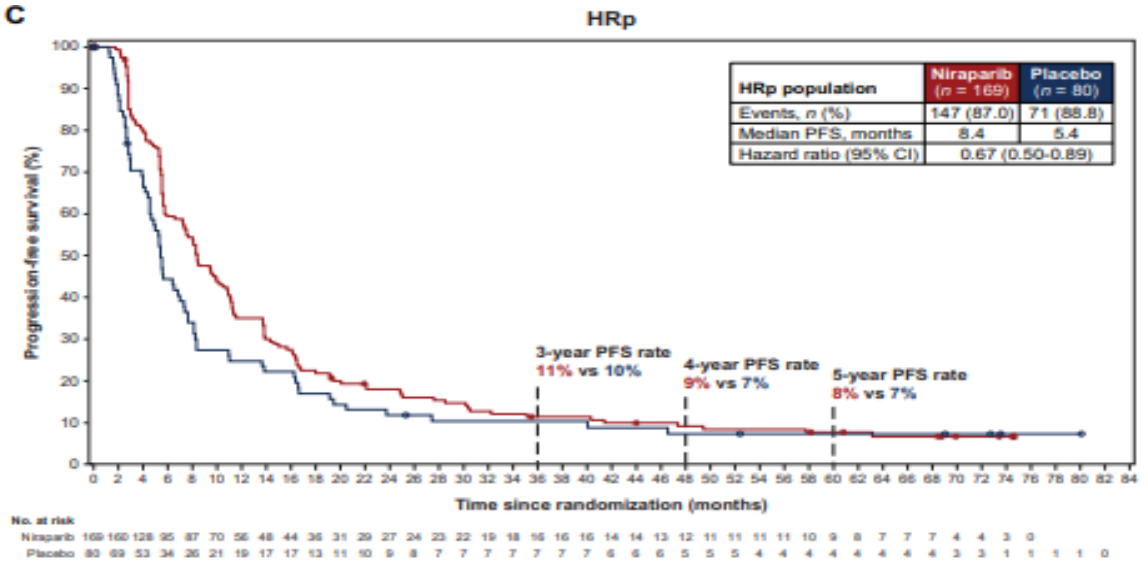
Despite the prognostic and predictive role of HRD testing, in 12-18% of cases, results are either inconclusive or borderline[7]

PRIMA/ENGOT-OV26/GOG-3012 trial

Updated long-term PFS (ad hoc, investigator-assessed)







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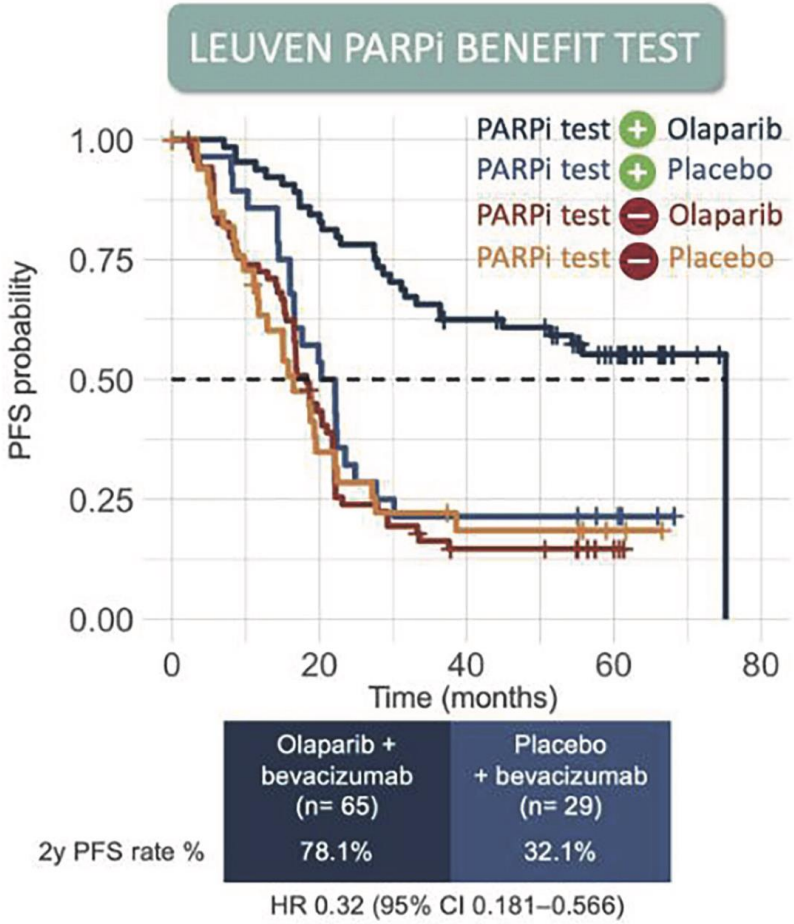
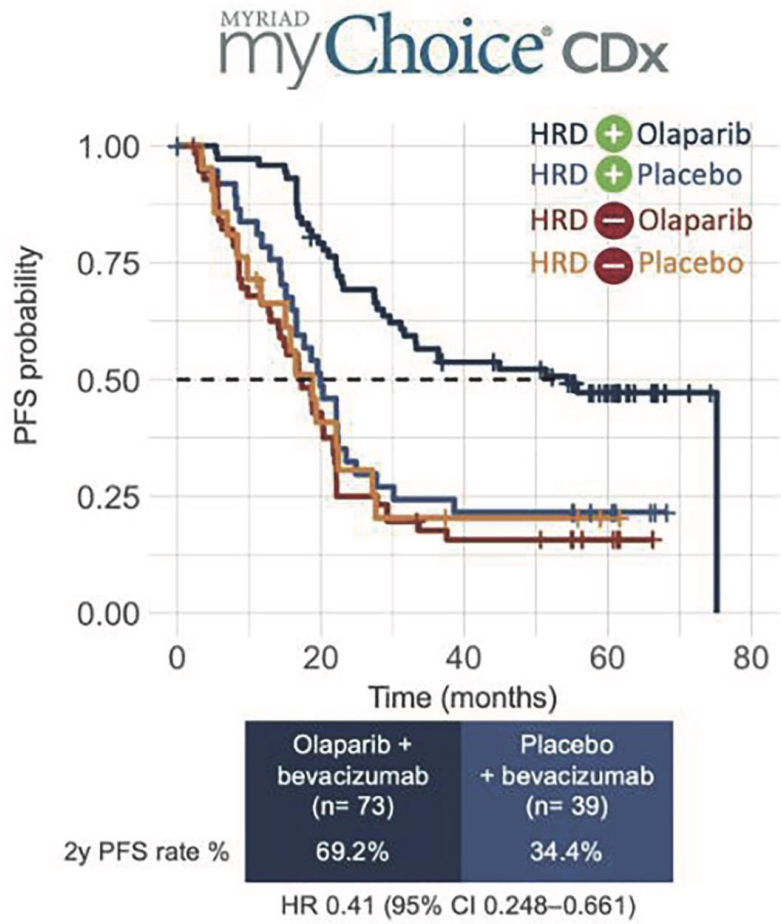
B Monk et al Ann Oncol 2024

Other test to predict PARPi response?

THE LEUVEN PARPi BENEFIT TEST

Genome-wide SNPs of the Leuven HRD test and mutation detection of BRCA1/2 coding exons sequenced with a custom-made capture panel.





Leuven PARPi Benefit Test → detection of benefit of PARPi in ovarian cancer patients suggesting a better predictive value compared with the Myriad test.

Liselore Loverix et al. Int J Gynecol Cancer 2024;34:A43-A44

Platinum responsiveness is a key predictive indicator of PARPi benefit

Response to platinum-based chemotherapy should be assessed after 3 cycles in different ways[1,2]:

- **Symptomatic response**
- **Radiological (RECIST)[1]**
- **Biochemical CA-125 (KELIM)[1]**
- **Pathological (CRS)[1]**

Ovarian cancer is a highly chemosensitive tumour. Approximately 70%-80% of patients respond to 1L platinum-based chemotherapy, with more than half achieving complete response[1]

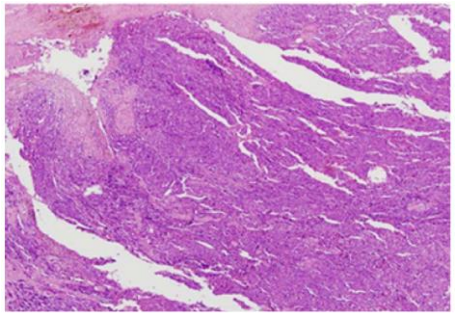
1L, first line; CA-125, cancer antigen 125; CRS, chemotherapy response score; HRd, homologous recombination deficiency; KELIM, CA-125 ELIMination rate constant K; PARPi, poly(ADP-ribose) polymerase inhibitor; RECIST, response evaluation criteria in solid tumour.

1. Caruso G, Tomao F, Parma G, et al. Int J Gynecol Cancer. 2023 Apr 3;33(4):431-43. 2. Ledermann JA, Raja FA, Fotopoulou C, et al; ESMO Guidelines Working Group. Ann Oncol. 2013 Oct;24 Suppl 6:vi24-32.

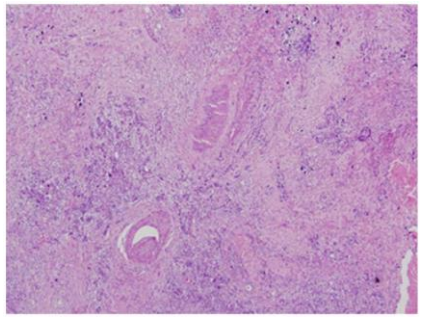
Pathological CRS

Ovarian tissue pathology with CRS of 1–3[1]

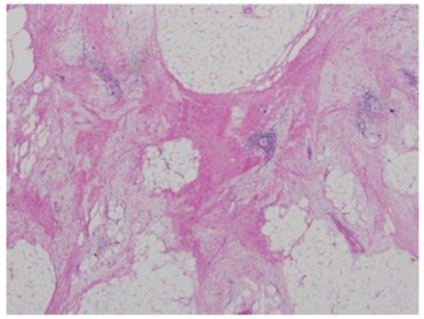
CRS 1



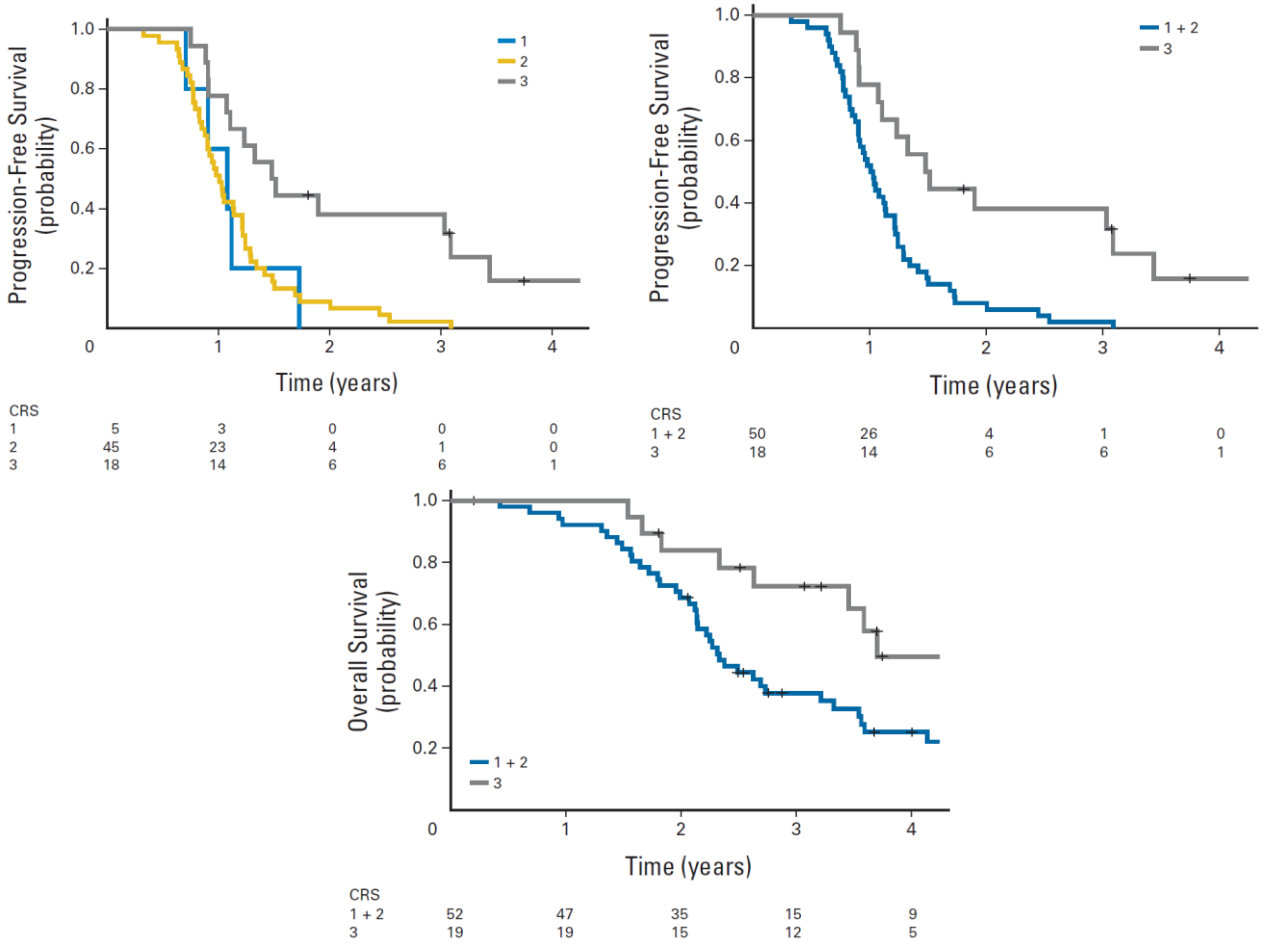
CRS 2



CRS 3



PFS and OS by CRS[2]

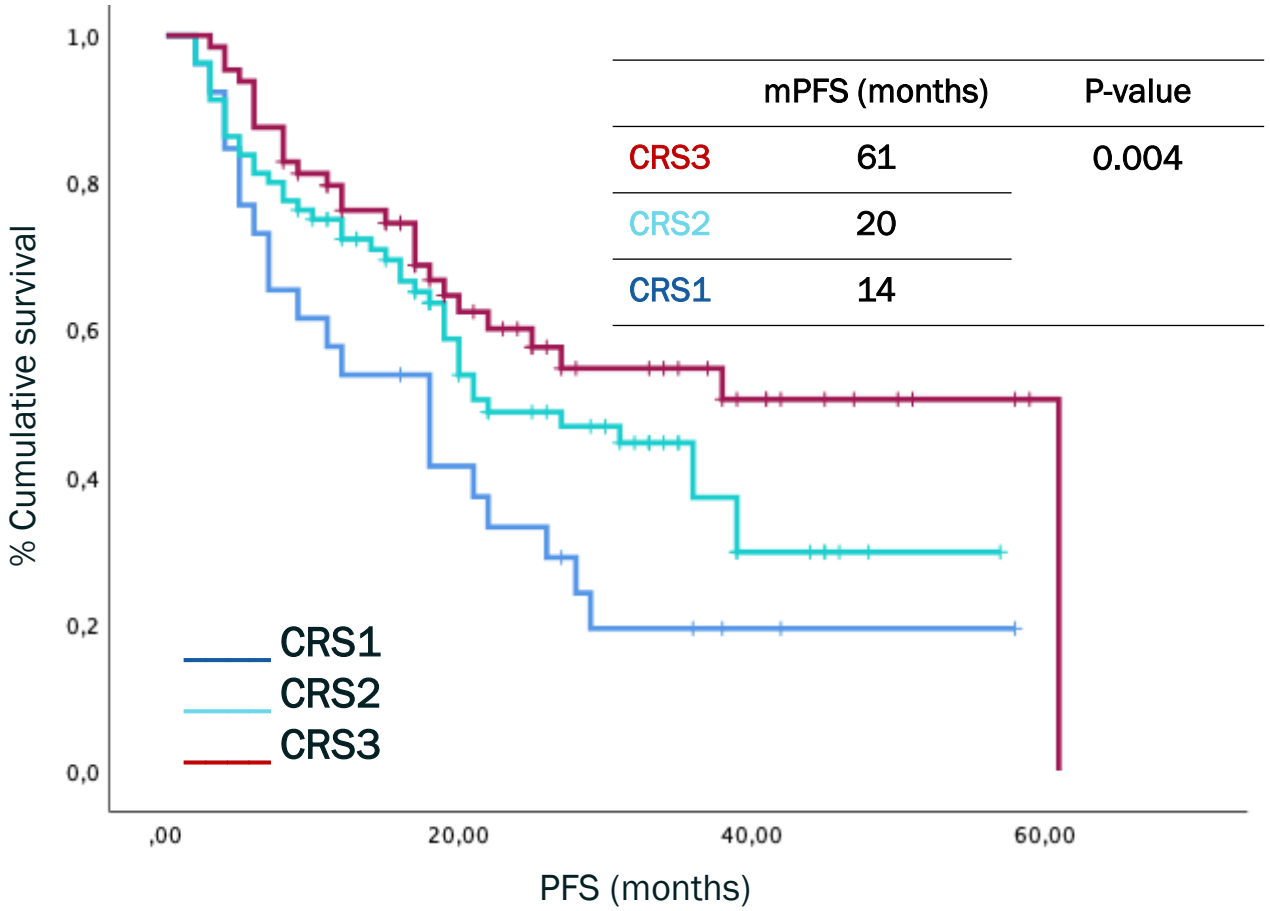


CRS, chemotherapy response score; OS, overall survival; PFS, progression-free survival

1. Michaan N et al., Int J Gyn Cancer. 2018;28:1676–82; 2. Bohm S et al., *J Clin Oncol*. 2015;33:2457–63

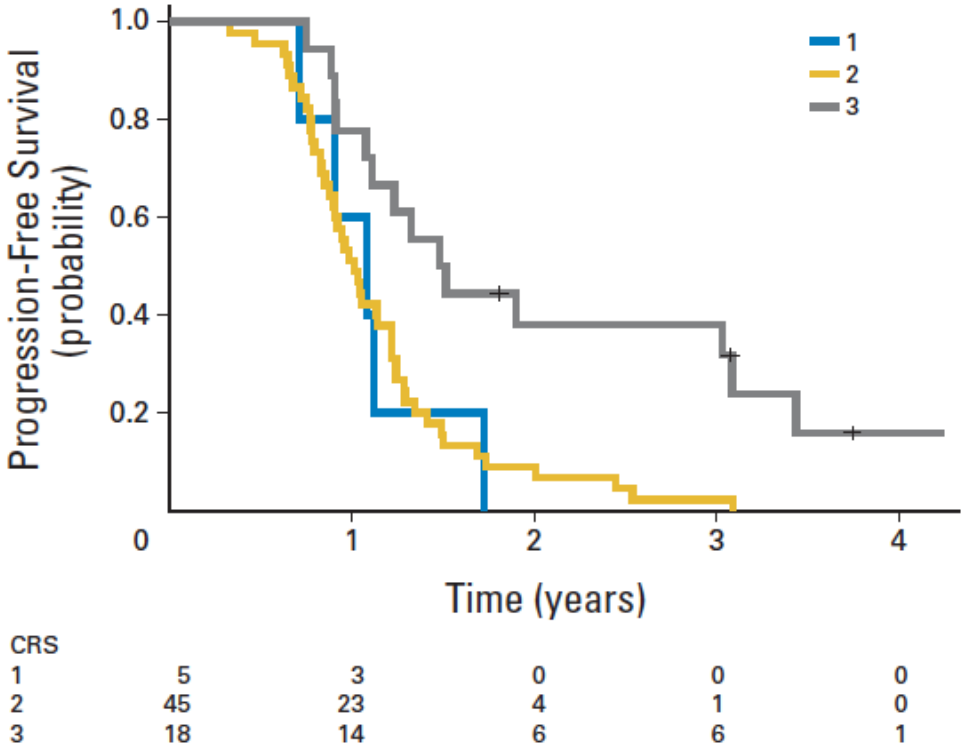
Is CRS correlated with PARPi response

PFS by CRS score[1]



	mPFS (months)	P-value
CRS3	61	0.004
CRS2	20	
CRS1	14	

PFS by CRS score[2]



CRS					
1	5	3	0	0	0
2	45	23	4	1	0
3	18	14	6	6	1

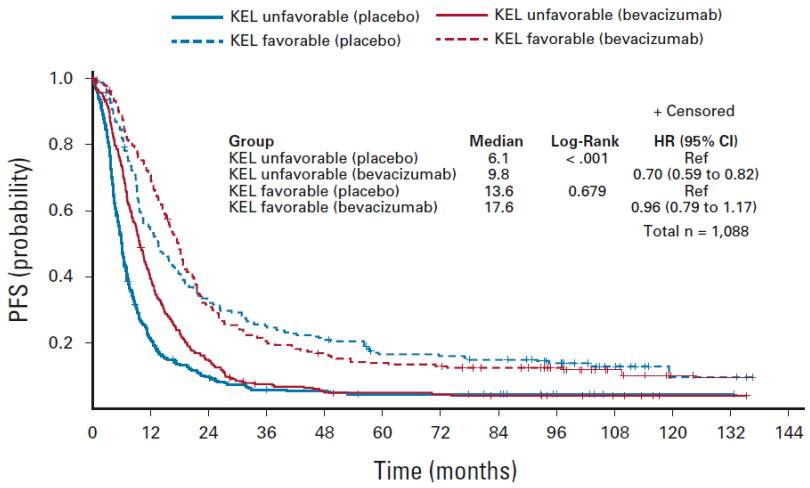
CRS, chemotherapy response score; mPFS, median PFS; PFS, progression-free survival; PARPi, poly(ADP-ribose)polymerase inhibitor

1. Gemelli, data-on-file; 2. Bohm S, et al. *J Clin Oncol.* 2015;33:2457

Disease characteristics: response to PBC and bevacizumab

Identification of Patients With Ovarian Cancer Experiencing the Highest Benefit From Bevacizumab in the First-Line Setting on the Basis of Their Tumor-Intrinsic Chemosensitivity (KELIM): The GOG-0218 Validation Study

PFS by favourability of KELIM score

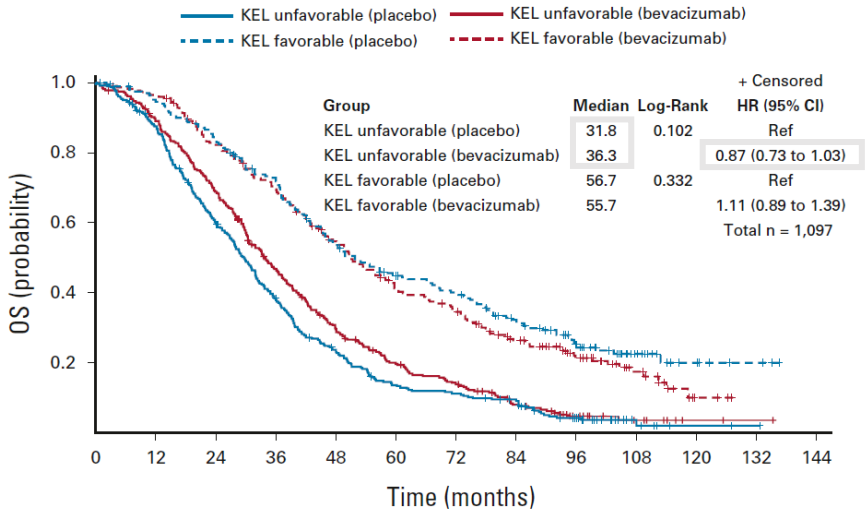


No. at risk:

KEL unfavorable (placebo)	327	18	12	1	0
KEL unfavorable (bevacizumab)	304	20	11	5	0
KEL favorable (placebo)	218	54	32	10	0
KEL favorable (bevacizumab)	239	48	30	7	0

3.7-month PFS†

OS by favourability of KELIM score



No. at risk:

KEL unfavorable (placebo)	330	137	54	7	0
KEL unfavorable (bevacizumab)	308	150	55	8	0
KEL favorable (placebo)	218	156	88	20	0
KEL favorable (bevacizumab)	241	168	88	20	0

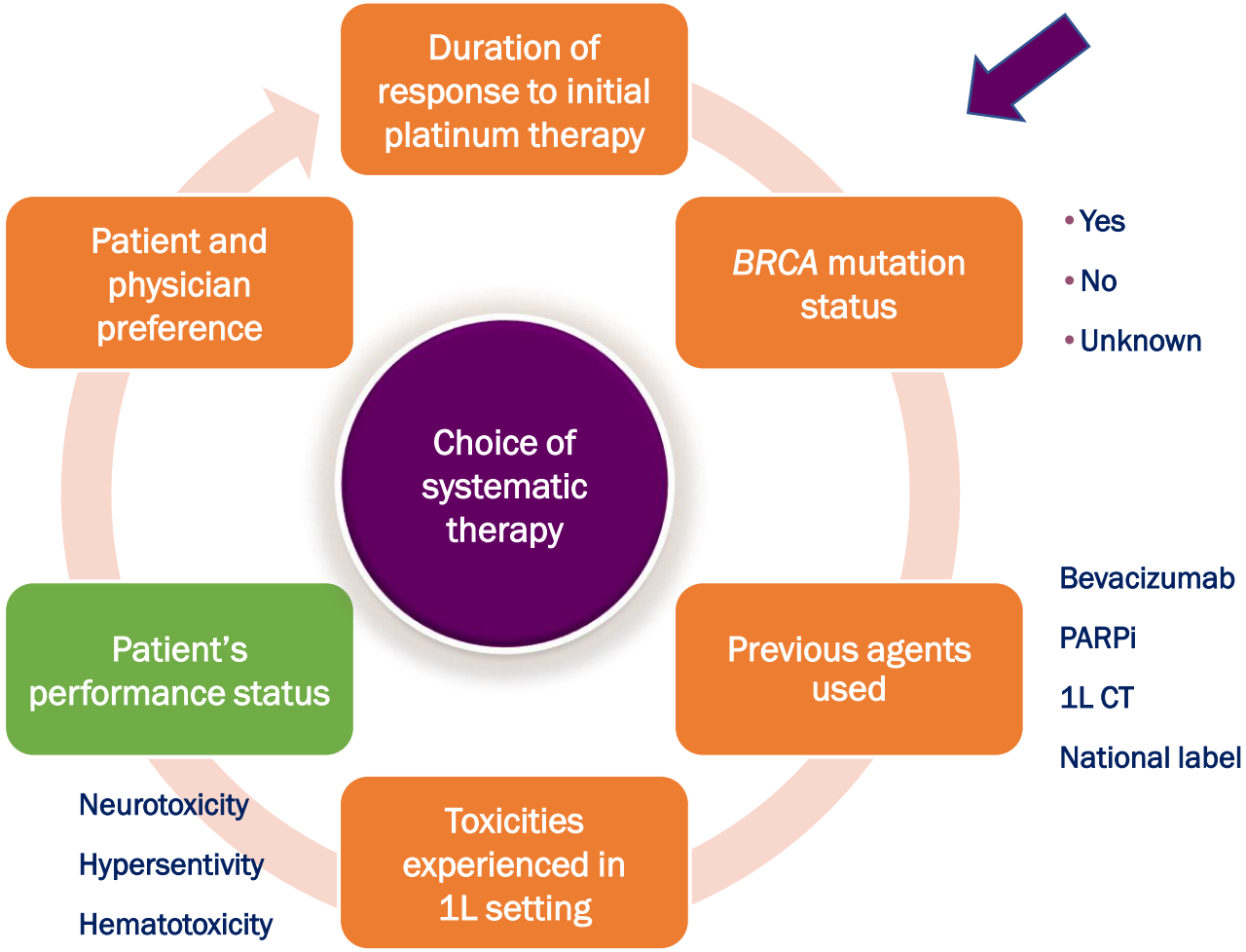
No statistically significant OS differences were observed in patients with unfavourable KELIM scores, and there were no correlations with HRR and *BRCA*m†

†Speaker commentary

*BRCA*m, *BRCA* mutant; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; KEL/KELIM, elimination rate constant K; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; Ref, reference

Benoit Y. et al., *J Clin Oncol.* 2022;40:3965-74.

Key factors involved in selecting systemic treatments



1L, first-line; CT, chemotherapy; PARPi, poly(ADP-ribose)polymerase inhibitor
Diagram summarises speaker's insights

The efficacy contribution of bevacizumab to maintenance PARPi has not been established in a randomised clinical trial

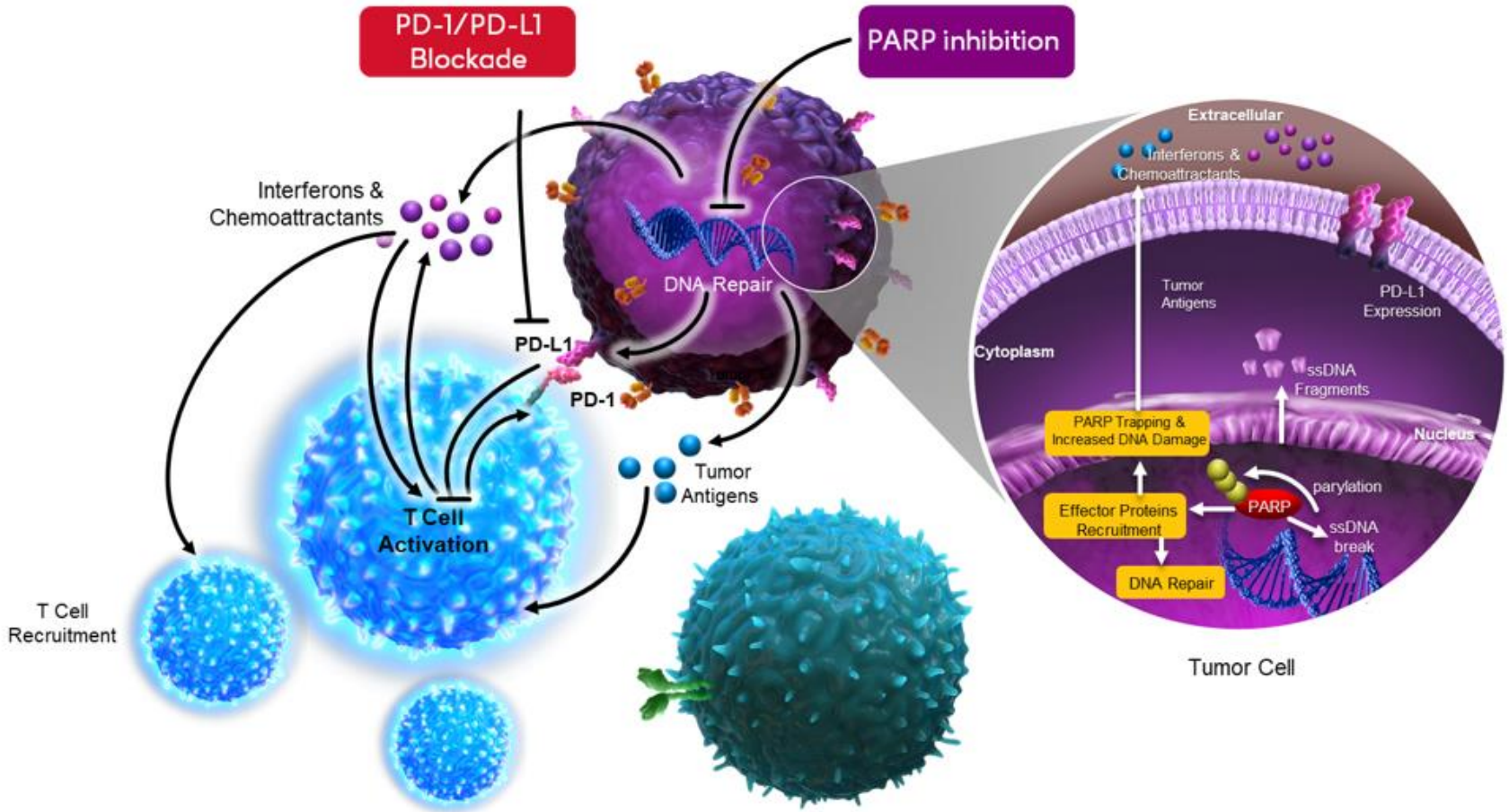
Future studies in 1Lm investigating use of bevacizumab

NIRVANA-1[1]	AGO-OVAR 28[2]	MITO25[3]
Niraparib with or without bevacizumab in maintenance after complete cytoreduction	Niraparib vs niraparib and bevacizumab as maintenance after platinum-based chemotherapy +/- bevacizumab	CT ± bevacizumab followed by rucaparib maintenance ± bevacizumab or bevacizumab alone

1Lm, first-line maintenance; Bev, bevacizumab; CT, chemotherapy; HRd, homologous recombination deficiency; mono, monotherapy; OC, ovarian cancer; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival. 1.. https://www.clinicaltrials.gov/ct2/show/NCT05183984; 2. https://clinicaltrials.gov/ct2/show/NCT05009082; 3. https://clinicaltrials.gov/ct2/show/NCT03462212; 5. https://ichgcp.net/clinical-trials-registry/NCT05460000 (Accessed: August 2022);

Rationale for PARP inhibition and IO in endometrial cancer

PARP inhibitors upregulate tumor cell PD-L1 expression, which may attenuate PARP inhibitor efficacy; therefore, PD-1/PD-L1 inhibition in combination with PARP inhibition may potentiate clinical efficacy[1]



cAMP = cyclic adenosine monophosphate; CCR9 = C-C chemokine receptor type 9; cGAS = cyclic GMP-AMP synthase; cGMP = cyclic guanosine monophosphate; CXCL9/10 = chemokine (C-X-C motif) ligand 9; DNA = deoxyribonucleic acid; dsDNA = double-stranded DNA; I-O = immuno-oncology; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; PARP = poly (ADP-ribose) polymerase; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1; STING = stimulator of interferon genes.

1. Jiao S et al. Clin Cancer Res. 2017;23:3711–3720. 2. Vikas P et al. Front Oncol 2020;10:570.

ATHENA STUDY

Key Patient Eligibility

- Newly diagnosed, stage III–IV, advanced, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; complete resection permitted)
- ECOG PS 0 or 1
- No prior frontline maintenance treatment for ovarian cancer

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors

- Tumor HRD test status[a]
- Disease status post-chemotherapy
- Timing of surgery

Treatment for 24 months,[b] with a 4-week lead-in of rucaparib; study drugs could be discontinued independently

Study Analyses

ATHENA-COMBO

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

ATHENA-MONO

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

Primary endpoint: Investigator-assessed PFS in the ITT population

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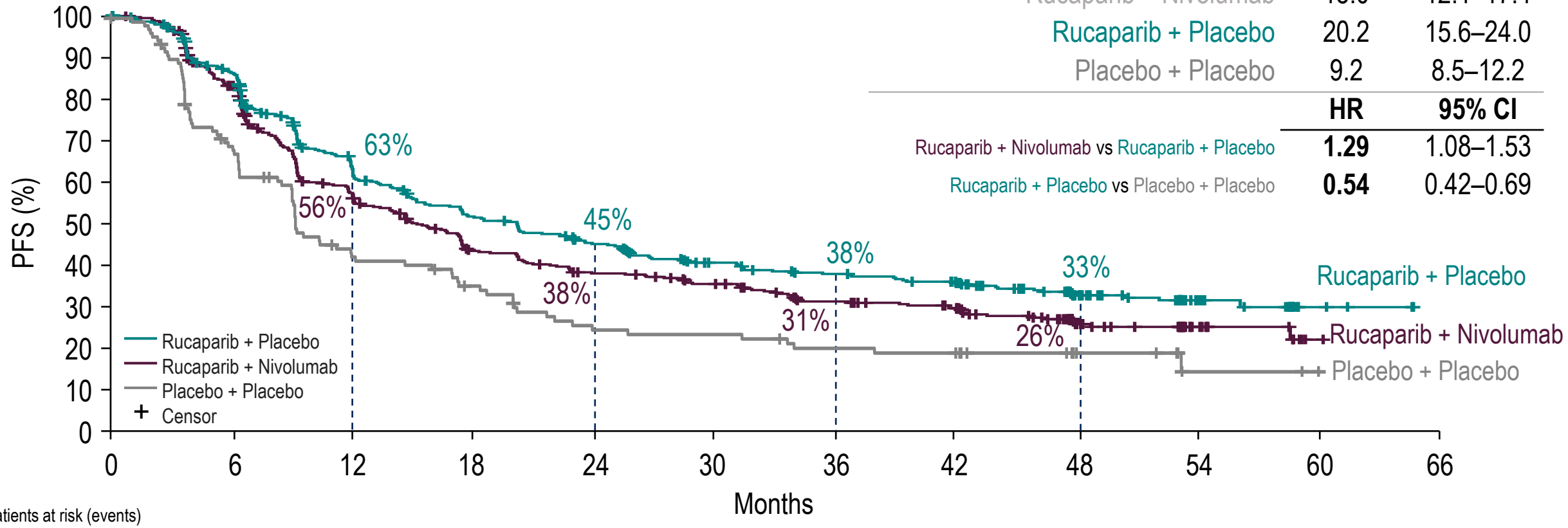
NCT03522246. [a]Centrally assessed, determined by FoundationOne CDx next-generation sequencing assay (BRCA mutation, BRCA wild-type/LOH high [LOH ≥16%], BRCA wild-type/LOH low [LOH <16%], BRCA wild-type/LOH indeterminate). [b]Treatment for 24 months or until radiographic progression, unacceptable toxicity, or other reason for discontinuation. IV placebo was intended to commence on Day 1 of Cycle 2 and treatment cap defined as 24 months after the start of IV placebo; 28-day cycles.
BID, twice daily; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; LOH, loss of heterozygosity; PFS, progression-free survival; PO, by mouth; PR, partial response.

ATHENA-COMBO: INVESTIGATOR-ASSESSED PFS (ITT)

	Median	95% CI
Rucaparib + Nivolumab	15.0	12.1–17.4
Rucaparib + Placebo	20.2	15.6–24.0
Placebo + Placebo	9.2	8.5–12.2
	HR	**95% CI**
Rucaparib + Nivolumab vs Rucaparib + Placebo	**1.29**	1.08–1.53
Rucaparib + Placebo vs Placebo + Placebo	**0.54**	0.42–0.69



Patients at risk (events)

Ruca+Nivo	436 (0)	333 (69)	218 (174)	159 (224)	136 (244)	122 (253)	98 (267)	87 (272)	44 (280)	14 (282)	1 (283)	0 (283)
Ruca+Plac	427 (0)	352 (57)	246 (149)	197 (193)	166 (218)	136 (234)	123 (243)	113 (249)	68 (258)	24 (260)	4 (261)	0 (261)
Plac+Plac	111 (0)	73 (34)	43 (61)	33 (69)	23 (78)	21 (80)	17 (83)	16 (84)	8 (84)	2 (85)	1 (85)	0 (85)

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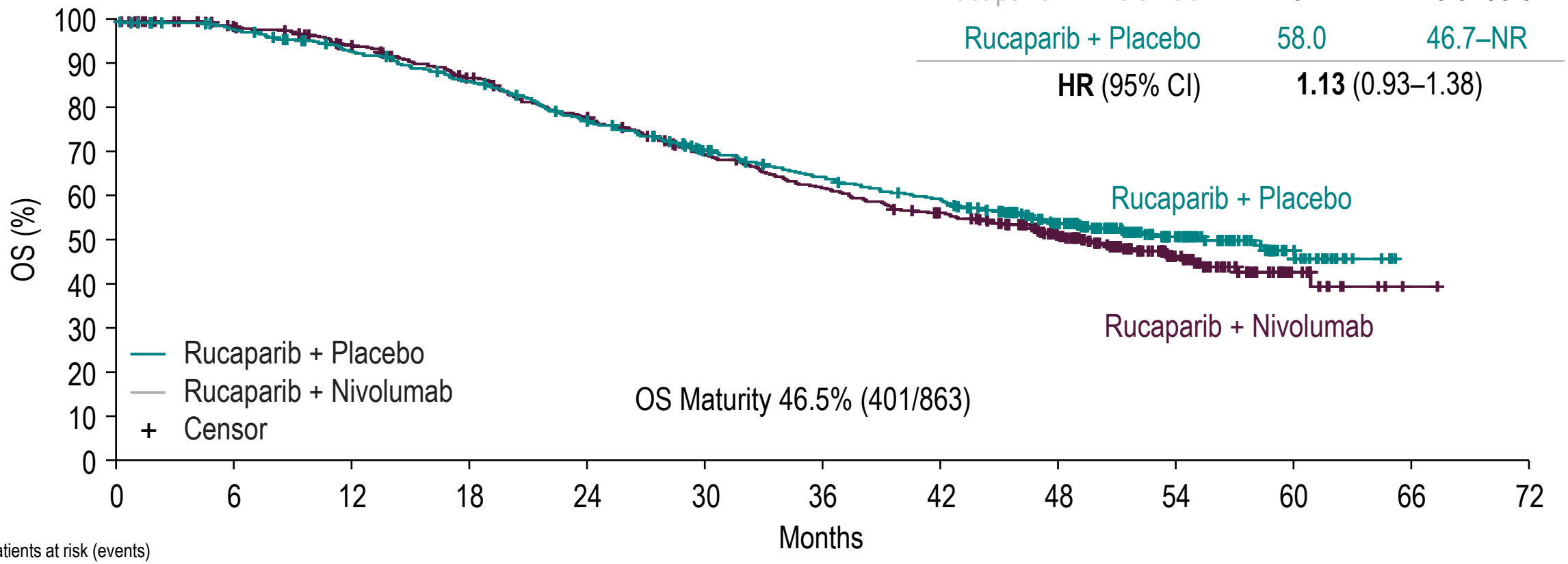
Data cutoff date: May 17, 2024.

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Nivo, nivolumab; PFS, progression-free survival; Plac, placebo; Ruca, rucaparib.

ATHENA-COMBO: INTERIM OS (ITT)

	Median	95% CI
Rucaparib + Nivolumab	49.4	43.9–55.3
Rucaparib + Placebo	58.0	46.7–NR
HR (95% CI)	**1.13** (0.93–1.38)	



Patients at risk (events)

Ruca+Nivo	436 (0)	413 (6)	388 (23)	351 (53)	312 (89)	272 (123)	242 (152)	214 (174)	153 (193)	66 (203)	17 (207)	1 (208)	0 (208)
Ruca+Plac	427 (0)	411 (8)	383 (29)	353 (57)	312 (94)	275 (120)	248 (143)	225 (164)	162 (182)	81 (189)	22 (193)	0 (193)	

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Data cutoff: May 17, 2024.

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Nivo, nivolumab; NR, not reached; OS, overall survival; Plac, placebo; Ruca, rucaparib.

ATHENA-COMBO SAFETY SUMMARY (SAFETY POPULATION)

Adverse Event, n (%)	Rucaparib + Nivolumab (n = 410)	Rucaparib + Placebo (n = 448)
Any-grade TEAE	407 (99.3)	435 (97.1)
Grade ≥3 TEAE	306 (74.6)	286 (63.8)
Oral drug treatment interruption and/or dose reduction due to TEAE	321 (78.3)	283 (63.2)
Discontinued oral study drug due to TEAE	104 (25.4)	66 (14.7)
Discontinued IV study drug due to TEAE	145 (35.4)	43 (9.6)
Discontinued oral and IV study drugs due to TEAE	63 (15.4)	19 (4.2)
Deaths[a] due to TEAE (excluding disease progression)	9 (2.2)	4 (0.9)
MDS/AML	4 (0.98)	4 (0.89)

- The most common TEAEs (≥2%) leading to discontinuation of oral and/or IV study drug were increased ALT/AST[b], anemia[b], asthenia[b], neutropenia[b], thrombocytopenia[b], febrile neutropenia, rash, and nausea
- MDS/AML rates were <1% in both arms; all events occurred in long-term follow-up except one event of MDS in the rucaparib + placebo arm

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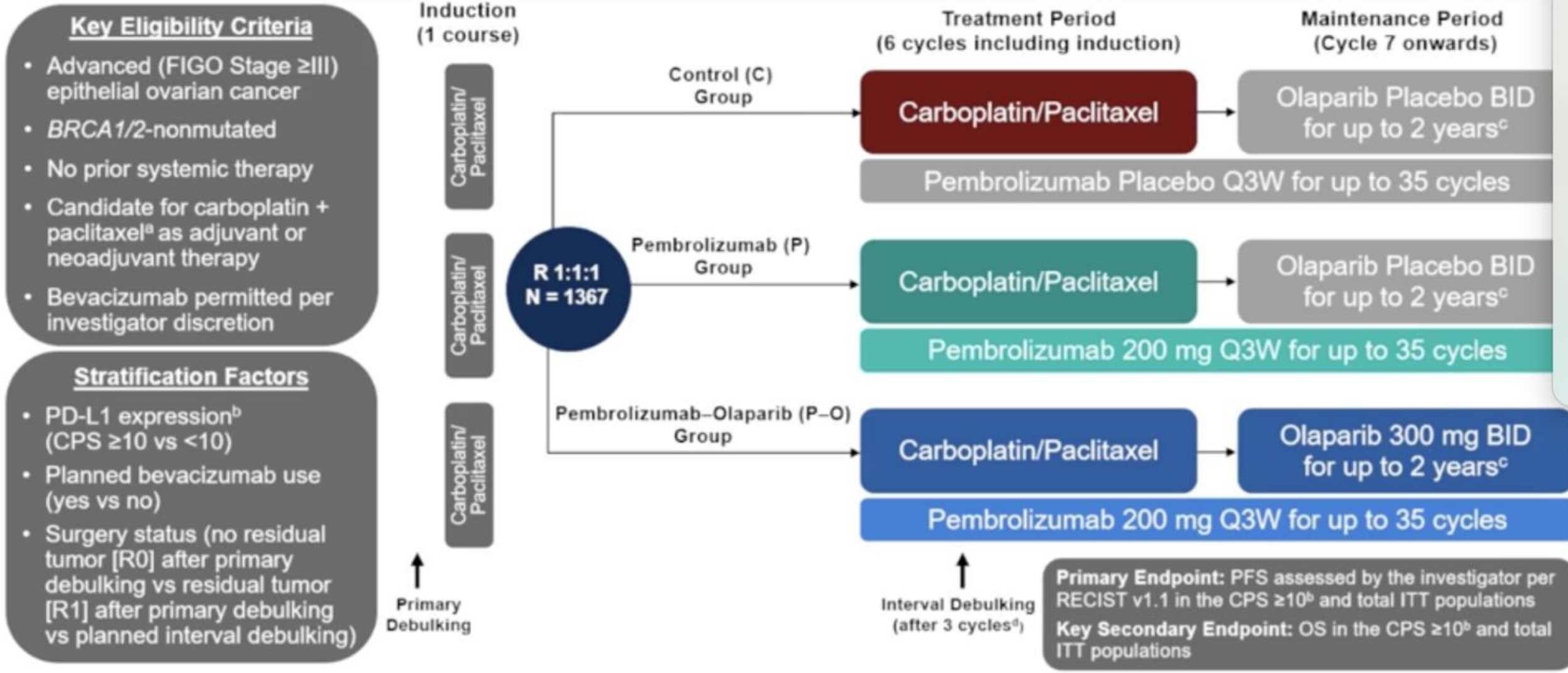
[a]Only 3 deaths were considered treatment-related, 2 in the rucaparib + nivolumab arm (febrile neutropenia and mega colon) and one in the rucaparib + placebo arm (AML); [b]Grouped terms: anemia or decreased hemoglobin, increased ALT or AST, asthenia or fatigue, neutropenia or decreased neutrophil count, thrombocytopenia or decreased platelet count.

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; IV, intravenous; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event (any adverse event with onset on or after the first dose of study medication until the latter of last oral + 28 days or last IV + 5 months).

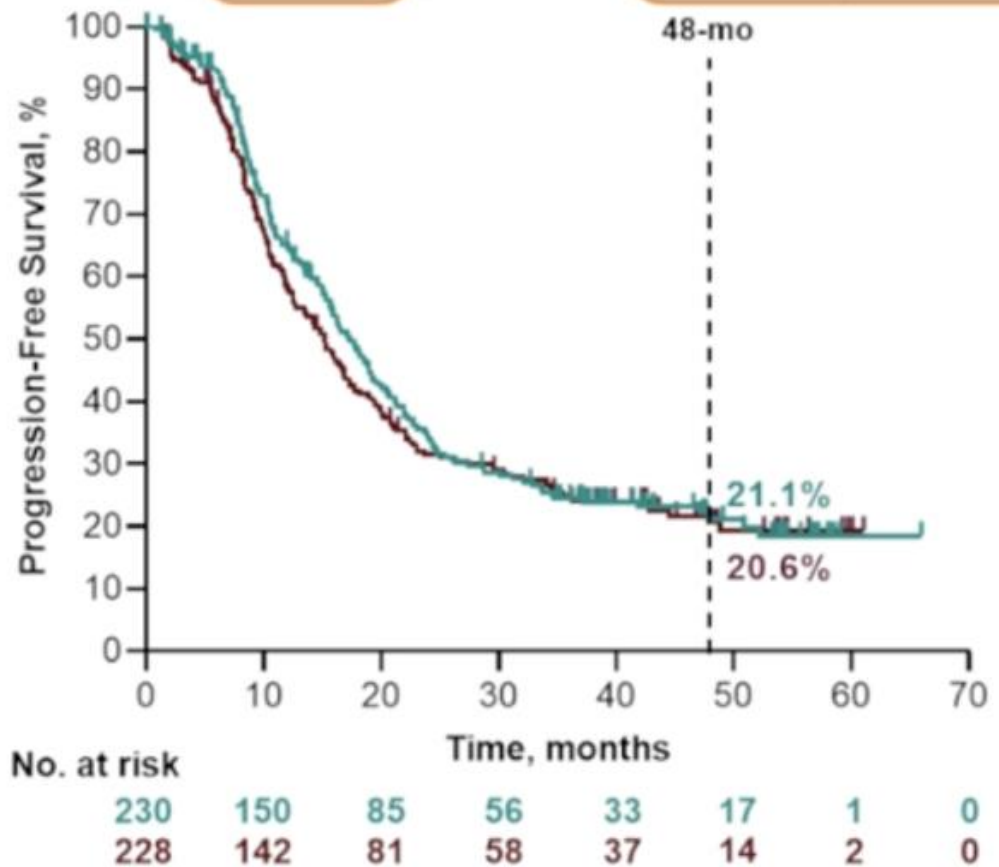
ENGOT-OV43/GOG-3036/KEYLYNK-001 Study Design (NCT03740165)



[a]Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an adverse event requiring discontinuation of paclitaxel. [b]Assessed

H3-4: Progression-Free Survival P vs C at FA in CPS ≥10 and Total ITT Populations

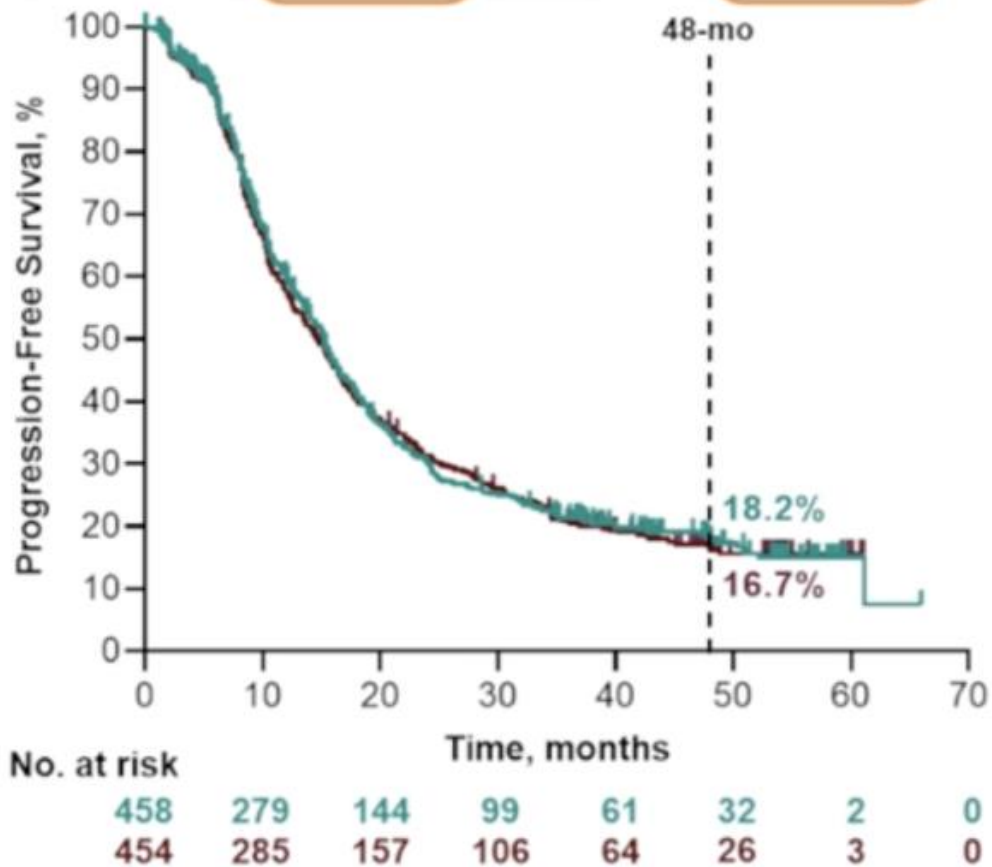
CPS ≥10 Population	Median, months	Events	HR (95% CI)	*P*-value
P Group	17.3	69.6%	0.95[a] (0.77-1.19)	0.3339[b]
C Group	15.2	72.4%		



No. at risk

230	150	85	56	33	17	1	0
228	142	81	58	37	14	2	0

Total ITT Population	Median, months	Events	HR (95% CI)
P Group	15.2	73.8%	1.01[a] (0.87-1.18)
C Group	14.6	77.5%	



No. at risk

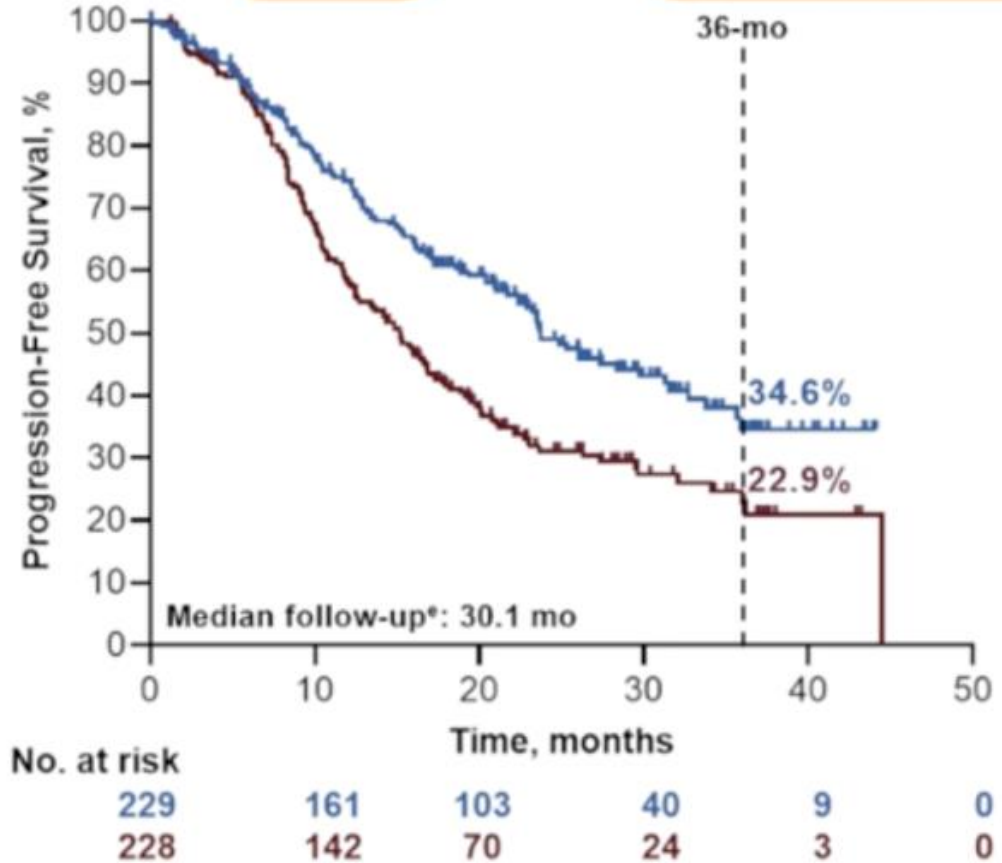
458	279	144	99	61	32	2	0
454	285	157	106	64	26	3	0

Median follow-up[c]: 49.6 mo

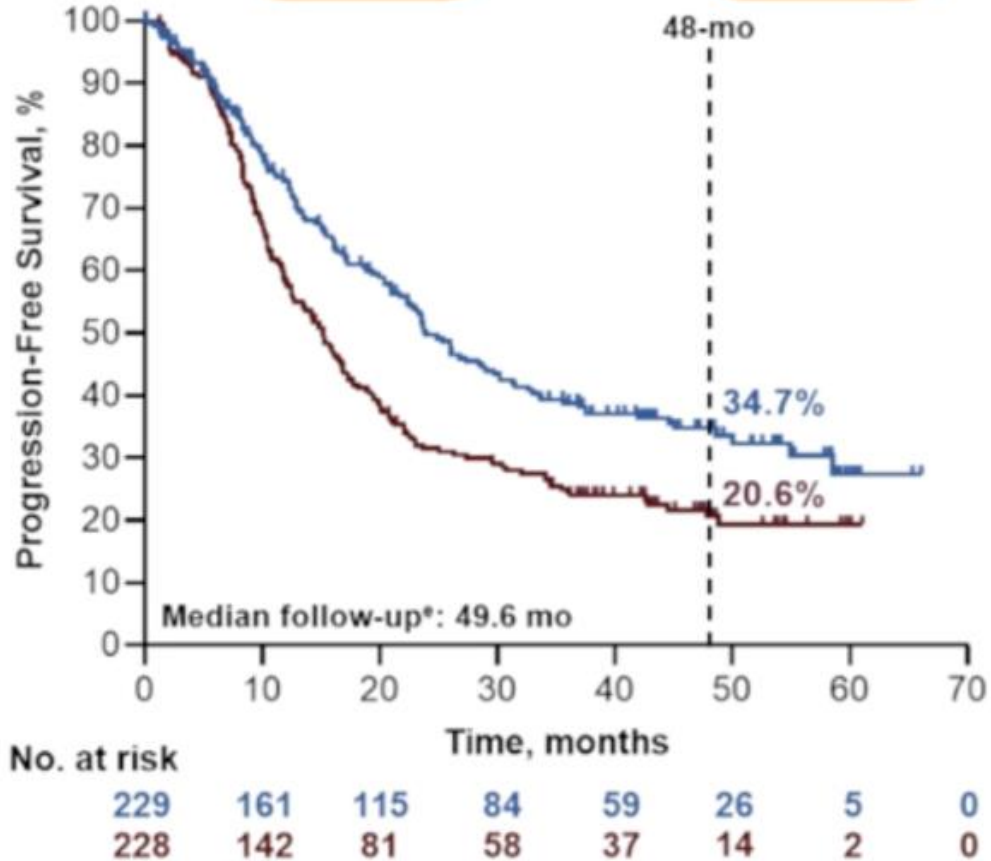
Response assessed per RECIST v1.1 by investigator review. [a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary not met. [c]Defined as the time from randomization to the data cutoff date. Data cutoff date: August 26, 2024.

H1: Progression-Free Survival P–O vs C, CPS ≥10 Population at IA1 and FA

IA1[a]	Median, months	Events	HR (95% CI)	*P*-value
P–O Group	23.7	48.9%	0.63[c] (0.49-0.80)	<0.0001[d]
C Group	15.2	66.2%		



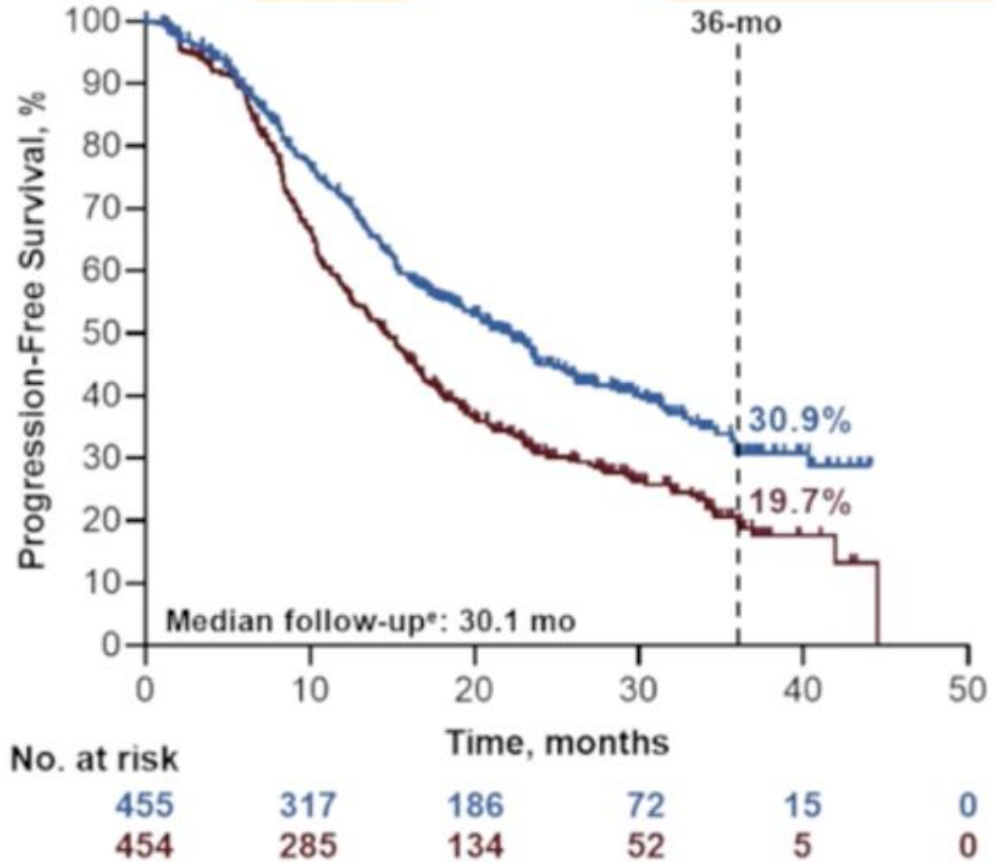
FA[b]	Median, months	Events	HR (95% CI)
P–O Group	23.9	58.5%	0.66[c] (0.53-0.83)
C Group	15.2	72.4%	



Response assessed per RECIST v1.1 by investigator review. [a]Data cutoff date: January 9, 2023. [b]Data cutoff date: August 26, 2024. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary met. [e]Defined as the time from randomization to the data cutoff date.

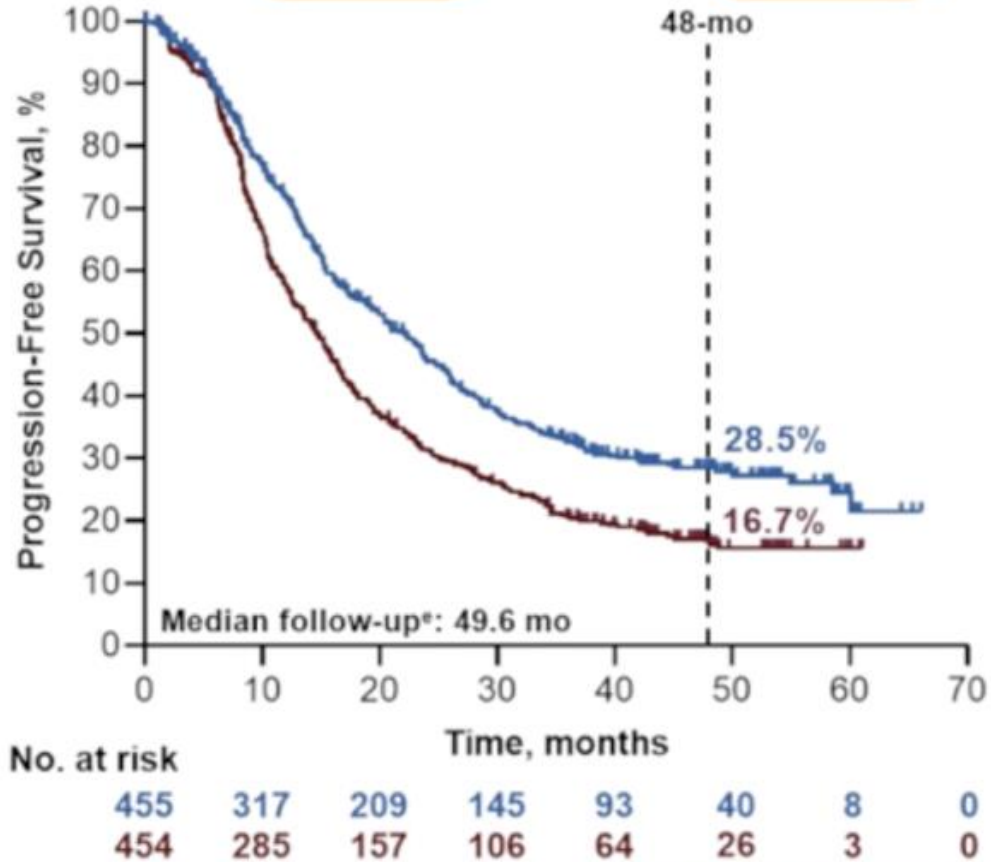
H2: Progression-Free Survival P–O vs C, Total ITT Population at IA1 and FA

IA1[a]	Median, months	Events	HR (95% CI)	*P*-value
P–O Group	22.1	53.0%	0.68[c] (0.58-0.81)	<0.0001[d]
C Group	14.6	69.2%		



No. at risk					
455	317	186	72	15	0
454	285	134	52	5	0

FA[b]	Median, months	Events	HR (95% CI)
P–O Group	22.2	64.0%	0.71[c] (0.61-0.84)
C Group	14.6	77.5%	



No. at risk							
455	317	209	145	93	40	8	0
454	285	157	106	64	26	3	0

Response assessed per RECIST v1.1 by investigator review. [a]Data cutoff date: January 9, 2023. [b]Data cutoff date: August 26, 2024. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary met. [e]Defined as the time from randomization to the data cutoff date.

Summary of Overall Survival and Post-Progression Therapy at FA

Overall Survival	P–O Group	C Group
CPS ≥10 Population		
Median, mo	50.2	51.6
HR (95% CI)	0.98 (0.75-1.27)	
Total ITT Population		
Median, mo	47.7	47.1
HR (95% CI)	1.04 (0.87-1.25)	

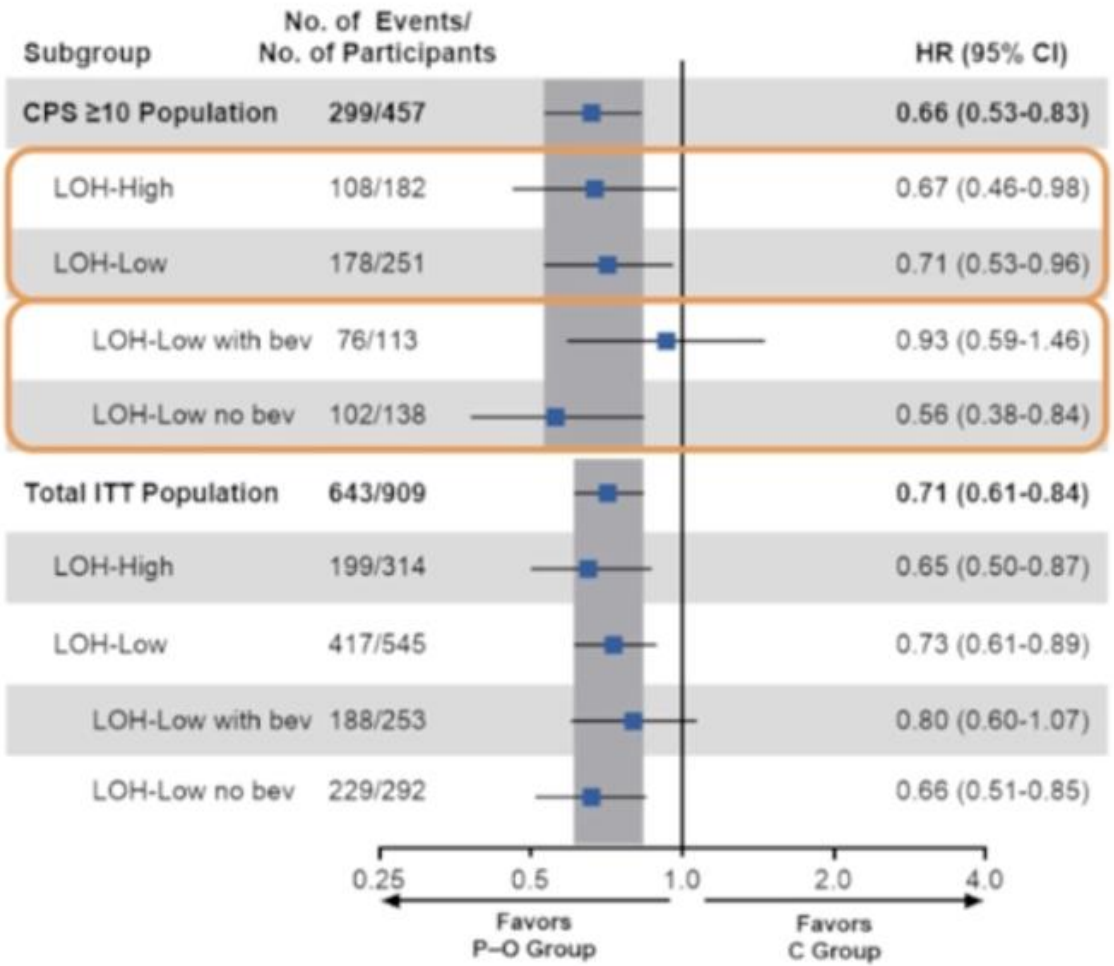
Overall Survival	P Group	C Group
CPS ≥10 Population		
Median, mo	56.4	51.6
HR (95% CI)	0.94 (0.72-1.22)	
Total ITT Population		
Median, mo	44.2	47.1
HR (95% CI)	1.06 (0.89-1.27)	

Post-Progression Therapy[a]	P–O Group (N = 291)	P Group (N = 338)	C Group (N = 352)
PARP inhibitors, n (%)	10 (3.4%)	50 (14.8%)	62 (17.6%)
Immunotherapy, n (%)	4 (1.4%)	6 (1.8%)	20 (5.7%)

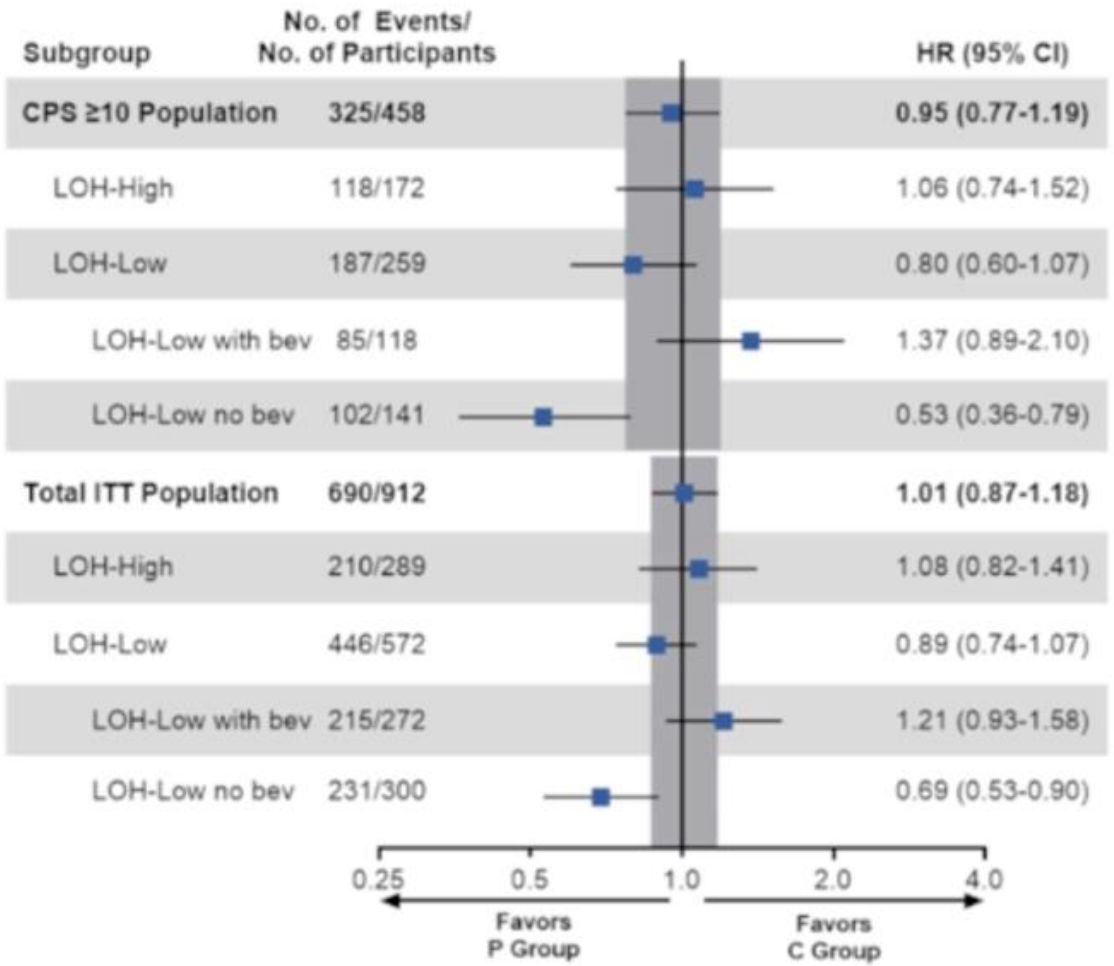
[a]All lines. Data cutoff date: August 26, 2024.

Progression-Free Survival in FMI-LOH Subgroups at FA

P–O vs C



P vs C



Response assessed per RECIST v1.1 by investigator review. FMI-LOH and bev subgroups based on post-hoc, exploratory, unstratified analysis. FMI, Foundation Medicine Inc. LOH, loss of heterozygosity. Bev, bevacizumab. Data cutoff date: August 26, 2024.

CONCLUSIONS

- Maintenance therapy with PARPis has demonstrated clinically meaningful improvements in PFS and OS in newly diagnosed advanced OC, with the greatest benefit in patients with HRd tumours
- Emerging long-term efficacy data from PARPi trials represents a milestone in OC management and highlights the potential for cure following maintenance PARPi in newly diagnosed advanced OC patients.
- However, the generation of increased platinum-resistance by PARPi, needs to be considered as negative mechanistic effects and the identification of post PARP effective agents is a priority of clinical research
- But over a decade there has been a large increase in the median survival of recurrent ovarian cancer- if not due to PARP inhibitors, then what else?
- The role of immunotherapy in OC, alone or in combination with PARPs is still controversial