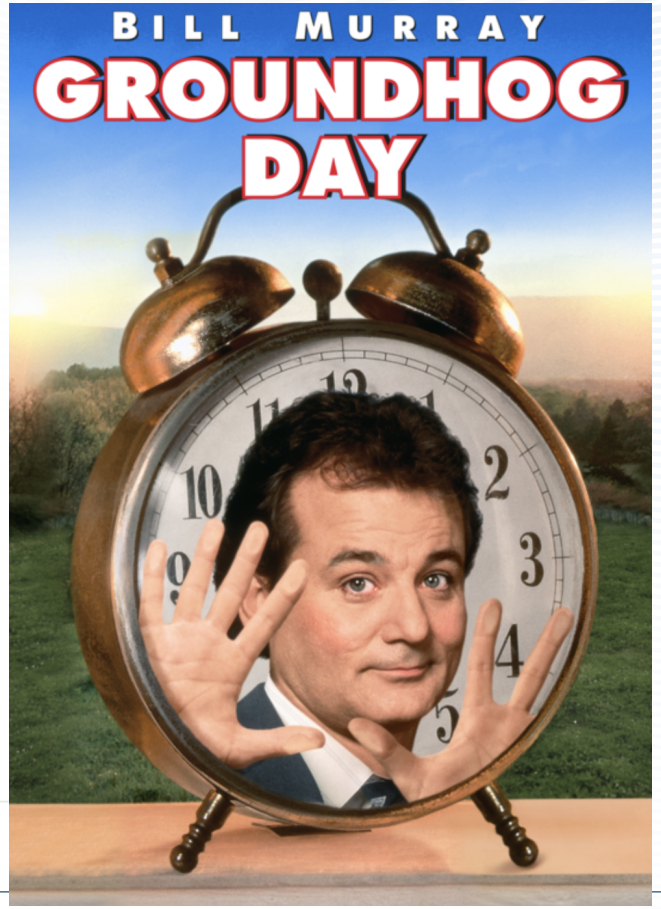
¡HAZ EL TEST!

HRD +: ¿APORTA ALGO EL BEVACIZUMAB? ¿CUÁL ES EL MEJOR ENFOQUE TERAPÉUTICO?

Eluska Iruarrizaga. Hospital Universitario de Cruces. Sº Oncología Médica



16:10 - 16:30 **HRD+: ¿Aporta algo bevacizumab? ¿Cuál es el mejor enfoque terapéutico?**

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Servicio de Oncología Médica
Hospital Universitario de Cruces, Barakaldo

AGOSTO/2023

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

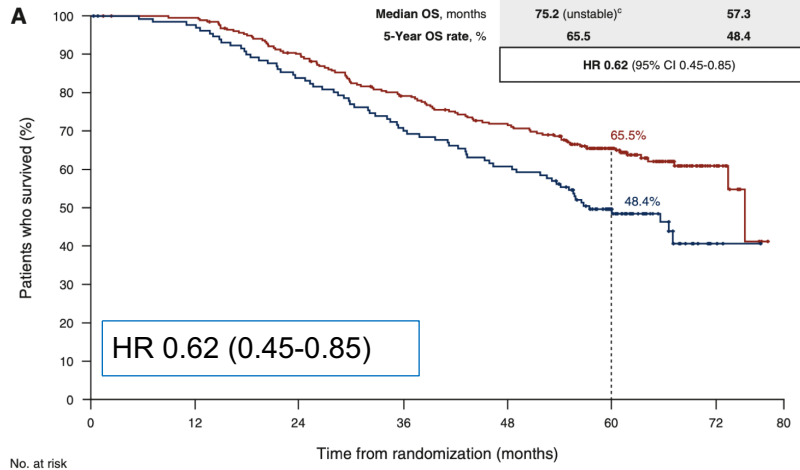
ORIGINAL ARTICLE

Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial

I. Ray-Coquard[1,2*], A. Leary[2,3], S. Pignata[4,5], C. Cropet[3,6], A. González-Martín[7,8], C. Marth[9,10], S. Nagao[11,12], I. Vergote[13,14], N. Colombo[15,16], J. Mäenpää[17,18], F. Selle[2,19], J. Sehouli[20,21], D. Lorusso[5,22], E. M. Guerra Alia[4,23], G. Bogner[10,24], H. Yoshida[12,25], C. Lefeuvre-Plesse[2,26], P. Buderath[21,27], A. M. Mosconi[5,28], A. Lortholary[2,29], A. Burges[21,30], J. Medioni[2,31], A. El-Balat[21,32,33], M. Rodrigues[2,34], T.-W. Park-Simon[21,35], C. Dubot[2,36], D. Denschlag[21,37], B. You[2,38], E. Pujade-Lauraine[39] & P. Harter[21,40], for the PAOLA-1/ENGOT-ov25 investigators†

BRCAmut

	Olaparib + bevacizumab (*N* = 255)	Placebo + bevacizumab (*N* = 132)
Events, *n* (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)[c]	**57.3**
5-Year OS rate, %	**65.5**	**48.4**
HR 0.62 (95% CI 0.45-0.85)		

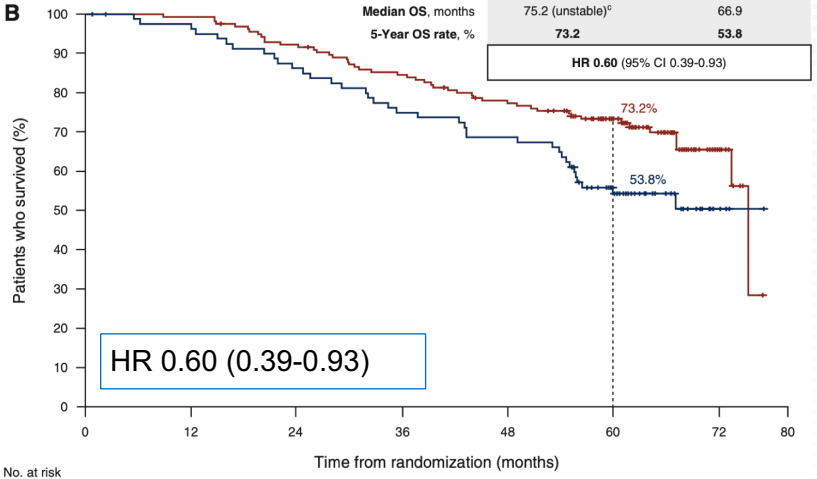


HR 0.62 (0.45-0.85)

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

HRD+

	Olaparib + bevacizumab (*N* = 157)	Placebo + bevacizumab (*N* = 80)
Events, *n* (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)[c]	66.9
5-Year OS rate, %	**73.2**	**53.8**
HR 0.60 (95% CI 0.39-0.93)		



HR 0.60 (0.39-0.93)

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

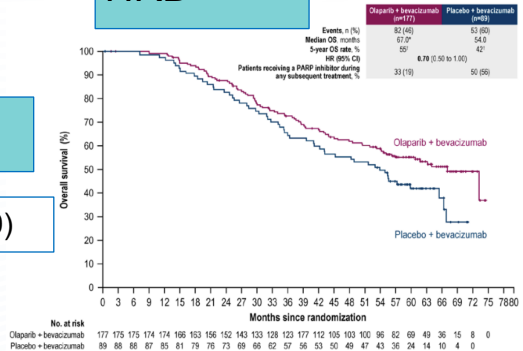
Ray-Coquard et al. Ann Oncol. 2023 Aug;34(8):681-692

DICIEMBRE/2023

HRD+

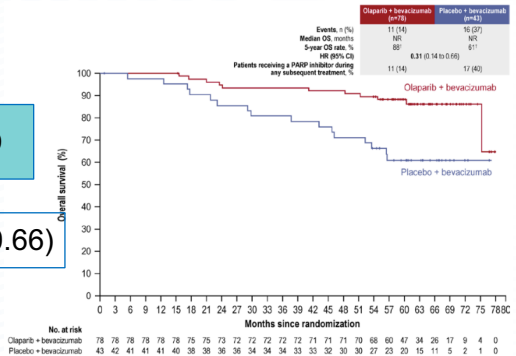
Alto riesgo

HR 0.7 (0.5-1.0)



Bajo riesgo

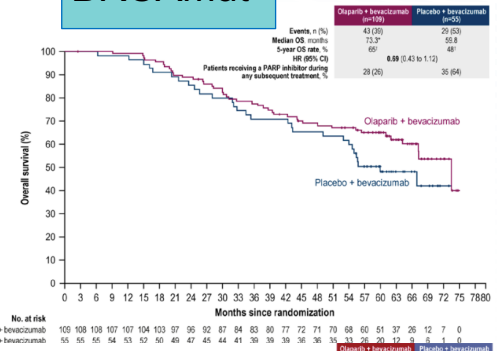
HR 0.31(0.14-0.66)



BRCAmut

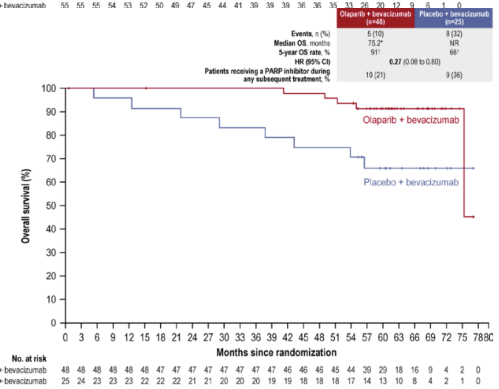
Alto riesgo

HR 0.69 (0.43-1.12)



Bajo riesgo

HR 0.27(0.06-0.8)



Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ ENGOT-ov25 trial

D. Lorusso et al. Int J Gynecol Cancer. 2024 Apr 1;34(4):550-558.

PAPEL DE BEVACIZUMAB EN CÁNCER DE OVARIO HRD+

PREMISA 1

Sólo 2 tratamientos de mantenimiento aprobados en mantenimiento en COA: Bevacizumab ó iPARP

PREMISA 2

Toda paciente HRD+ recibirá (a priori) un tratamiento de mantenimiento con iPARP

PREMISA 3

PAOLA-1 es el único EC que combina iPARP y bevacizumab de mantenimiento con resultados positivos (por el momento)

PAPEL DE BEVACIZUMAB EN CÁNCER DE OVARIO HRD+

PAPEL DE BEVACIZUMAB EN CÁNCER DE OVARIO HRD+

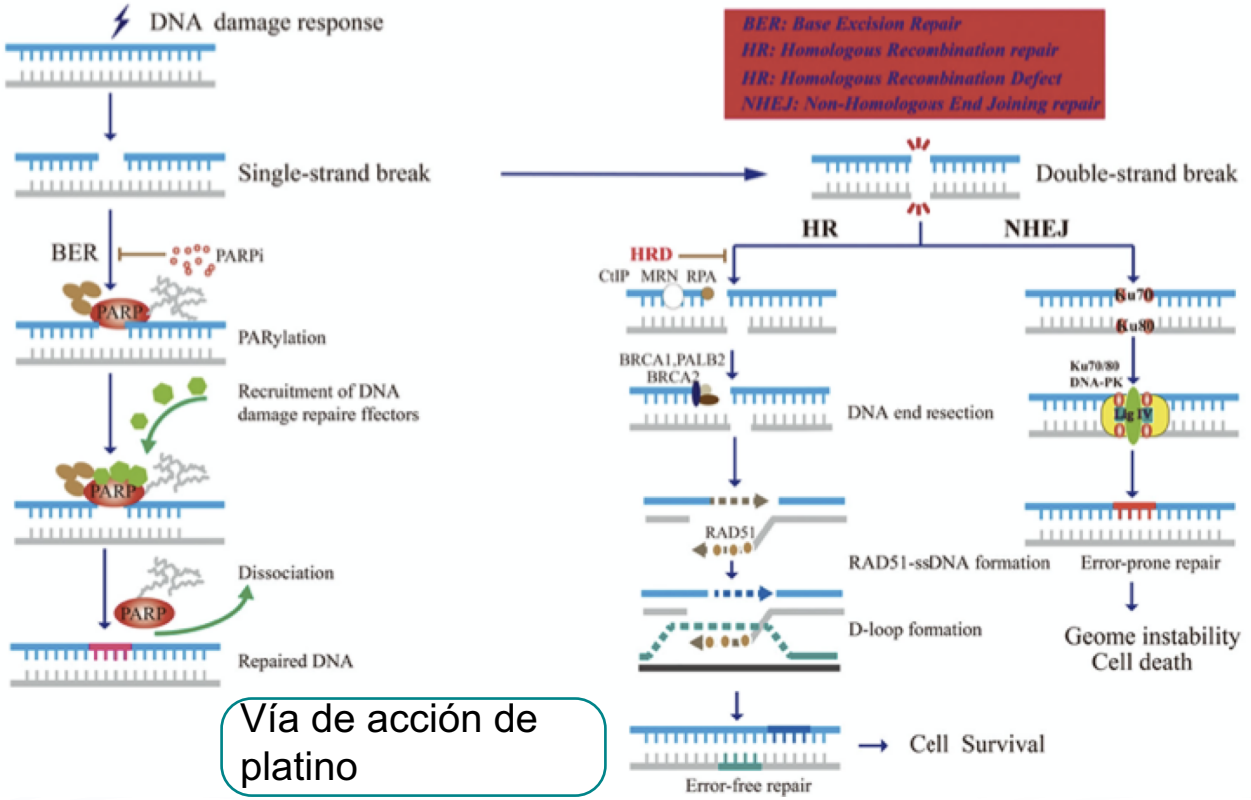
- ¿Qué es cáncer de ovario HRD?
- ¿Qué es cáncer de ovario de alto/bajo riesgo?
- Tratamientos de mantenimiento en primera línea en COA HRD+ (y evidencia):
    - Bevacizumab
    - iPARP
    - iPARP+Bevacizumab
- ¿Aporta algo Bevacizumab en pacientes HRD+?
    - Argumentos a favor
    - Argumentos en contra
- Conclusiones

¿QUÉ SIGNIFICA HRD+?
BIOMARCADOR PREDICTIVO DE RESPUESTA

Incapacidad de una célula para reparar eficazmente las roturas de doble cadena del ADN utilizando la vía de reparación por recombinación homóloga (HRR).

iPARP no es un tratamiento dirigido frente a HRD

HRD+: biomarcador predictivo de respuesta a iPARP/Platino



Vía de acción de platino

¿QUÉ SIGNIFICA HRD+? BIOMARCADOR PRONÓSTICO

Patients are classified as moderate risk if they have all of the following risk factors:

- Stage III disease
- BRCAm
- PCS
- No VRD

Patients are classified as high risk if they have ≥1 of the following risk factors:

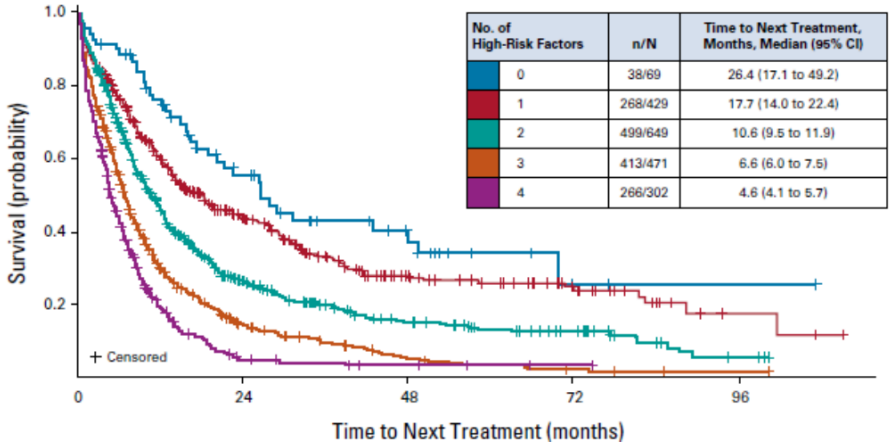
- Stage IV disease
- ICS or no surgery
- VRD or no surgery
- BRCAwt, BRCA unknown or BRCA missing
- Partial response to CT

La diferencia en los % de estas variables en EC condiciona la OS (independientemente del fármaco a estudio)

Bajo el mismo tratamiento, las pacientes de alto riesgo van a vivir menos que las pacientes de bajo riesgo

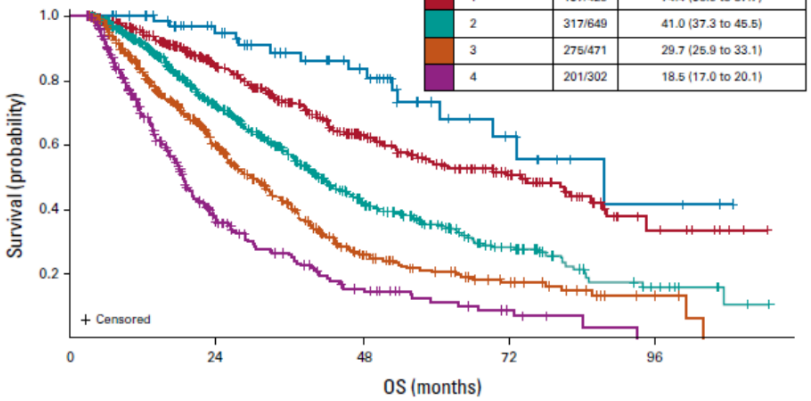
OS HRD+/BRCAmut > HRD+/BRCAwt > HRP

IMPACT OF THE ACCUM



No. of High-Risk Factors	n/N	Time to Next Treatment, Months, Median (95% CI)
0	38/69	26.4 (17.1 to 49.2)
1	268/429	17.7 (14.0 to 22.4)
2	499/649	10.6 (9.5 to 11.9)
3	413/471	6.6 (6.0 to 7.5)
4	266/302	4.6 (4.1 to 5.7)

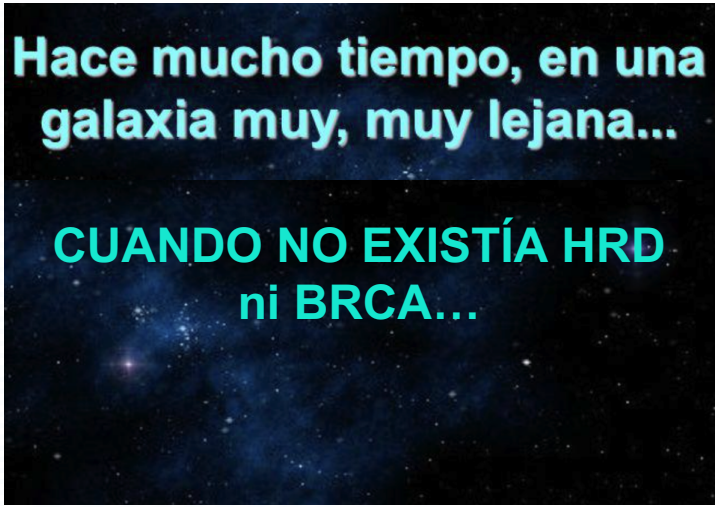
B



No. of High-Risk Factors	n/N	OS, Months, Median (95% CI)
0	15/69	87.8 (60.8 to not reached)
1	137/429	74.4 (56.9 to 87.7)
2	317/649	41.0 (37.3 to 45.5)
3	275/471	29.7 (25.9 to 33.1)
4	201/302	18.5 (17.0 to 20.1)

Chase D, Perhanidis J, Gupta D, Kalilani L, Golembesky A, González-Martín A. Association of Multiple High-Risk Factors on Observed Outcomes in Real-World Patients With Advanced Ovarian Cancer Treated With First-Line Therapy. JCO Clin Cancer Inform. 2023 Jun;7:e2200189

TRATAMIENTOS DE MANTENIMIENTO 1L COA



TRATAMIENTOS DE MANTENIMIENTO 1L COA: BEVACIZUMAB

ICON-7

- Pacientes con CO epitelial, de trompas de Falopio o peritoneal primario de nuevo diagnóstico
- ECOG 0-2
- Estadio FIGO IIb-IV (FIGO 1988) o estadio I-IIa de alto riesgo (grado 3 o histología de células claras).
- Sometidas a cirugía citorreductora primaria o inoperables

R 1:1

n=1528

n=764: Carboplatino AUC 5 o 6, d1 + Paclitaxel 175 mg/m², d1 — X 6 ciclos

n=764: Carboplatino AUC 5 or 6, d1 + Paclitaxel 175 mg/m², d1 + Bev 7,5 mg/kg, d1 (Bev se omite en el ciclo 1 si se inició la QT durante las 4 primeras semanas tras la cirugía) — X 6 ciclos

Repetición de ciclos cada 3 semanas

Bev 7,5 mg/kg cada 3 semanas X 12 ciclos o hasta progresión de enfermedad

Hasta 12 meses

Factores de estratificación:
- Grupo GCIG
- Estadio FIGO y enfermedad residual
- Intervalo planificado entre la cirugía y el inicio de la quimioterapia (≤4 semanas o >4 semanas)

Objetivo primario:
- Supervivencia libre de progresión

Objetivo secundario:
- Supervivencia global
- Intervalo libre de progresión bioquímica
- Tasa de respuesta
- Toxicidad
- Calidad de vida

GOG-0218

- Pacientes con CO epitelial, de trompas de Falopio o peritoneal primario de nuevo diagnóstico sometidas a cirugía citorreductora primaria
- Estadio III con enfermedad residual macroscópica ≤1cm
- Estadio III (>1 cm)
- Estadio IV

R 1:1:1

n=1873

Factores de estratificación:
- GOG performance status
- Estadio FIGO y resultado de la cirugía

n=625: QT sola — Carboplatino AUC 6 + Paclitaxel 175 mg/m² — Placebo X 22 ciclos

n=625: QT + Bev inducción — Carboplatino AUC 6 + Paclitaxel 175 mg/m² + Bev 15 mg/kg* — Placebo X 16 ciclos

n=623: QT + Bev mantenimiento — Carboplatino AUC 6 + Paclitaxel 175 mg/m² + Bev 15 mg/kg* — Bev 15 mg/kg** X 16 ciclos

Repetición de ciclos cada 21 días

Hasta 15 meses

Objetivo primario:

Supervivencia libre de progresión
- Evaluación del investigador por RECIST

Objetivo secundario:
- Supervivencia global
- Tasa de respuesta
- Seguridad
- Calidad de vida

Adaptado de Burger RA, et al. N Engl J Med. 2011. Material suplementario[1]

"Inducción Bevacizumab"; "" Mantenimiento Bevacizumab".

Bev: bevacizumab; D: día; FIGO: federación internacional de ginecología y obstetricia; GOG: Grupo de Ginecología Oncológica; RECIST: criterios de evaluación en Tumores Sólidos; QT: quimioterapia; AUC: área bajo de la curva; R: aleatorización; CO: cáncer de ovario.

Diferencias:

- Inclusión de pacientes: ICON 7 estadio I/II
- Nº de brazos: 2 vs 3
- Dosis de Bv: 7.5 mg/kg vs 15 mg/kg
- Tiempo de bevacizumab: 12 meses vs 15 meses

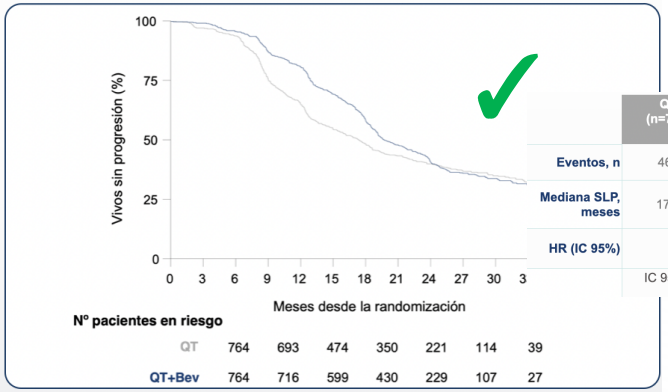
Similitudes:

- Factores de estratificación (estadio, end residual)
- Objetivos: 1º PFS/2º OS

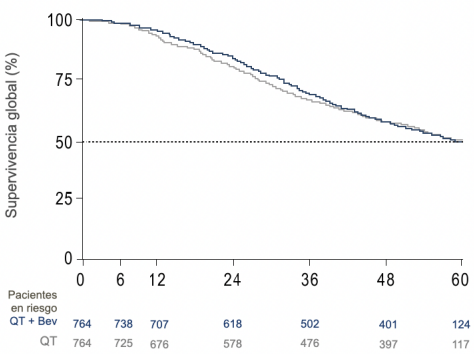
1. Oza ete a. ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):928-36. doi: 10.1016/S1470-2045(15)00086-8. Epub 2015 Jun 23.
2. Tewari et al. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. J Clin Oncol. 2019 Sep 10;37(26):2317-2328.

TRATAMIENTOS DE MANTENIMIENTO 1L COA: BEVACIZUMAB

ICON-7

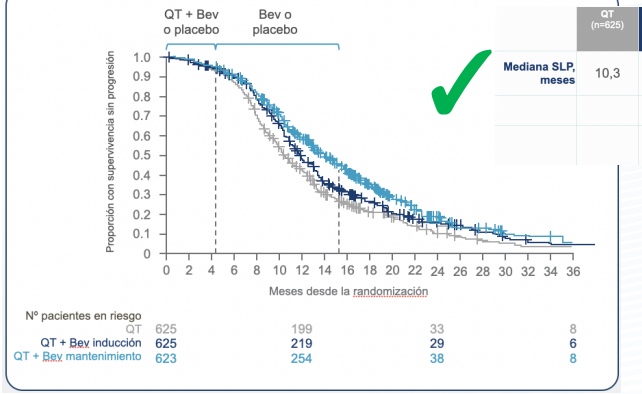


	QT (n=764)	QT + Bev (n=764)
Eventos, n	464	470
Mediana SLP, meses	17,4	19,8
HR (IC 95%)	HR 0,87	
	IC 95% (0,77–0,99); p=0,04	

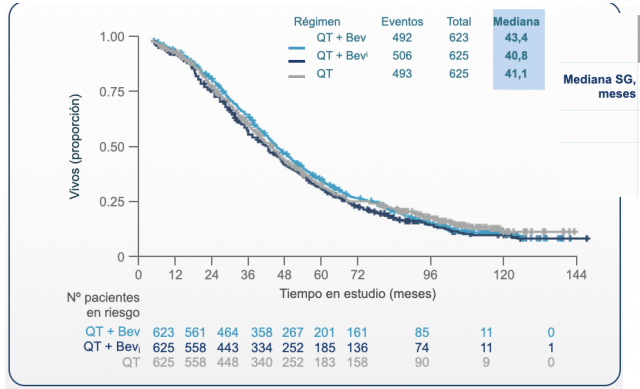


	QT (N=764)	QT+Bev (N=764)
Muertos, n	352	362
Mediana SG (meses)	58,6	58,0
HR (IC 95%)	HR 0,99	
	IC 95% (0,85-1,14); p=0,85	

GOG-0218



	QT (n=625)	QT + Bev inducción (n=625)	QT + Bev mantenimiento (n=623)
Mediana SLP, meses	10,3	11,2	14,1
		HR 0,908	HR 0,717
		IC 95%, (0,795–1,040); p=0,16	IC 95% (0,625–0,824); p<0,001



	QT (n=625)	QT + Bev inducción (n=625)	QT + Bev mantenimiento (n=623)
Mediana SG, meses	41,1	40,8	43,4
		HR 1,06	HR 0,96
		IC 95%, (0,94-1,20);p=0,34	IC 95% (0,85–1,09); p=0,53

1. Oza etc a. ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):928-36. doi: 10.1016/S1470-2045(15)00086-8. Epub 2015 Jun 23. 2.
Tewari et al. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. J Clin Oncol. 2019 Sep 10;37(26):2317-2328.

TRATAMIENTOS DE MANTENIMIENTO 1L COA: BEVACIZUMAB

A PESAR DE HABER CONSEGUIDO SU ENDPOINT 1º, FDA NO APRUEBA BEVACIZUMAB POR NO IMPACTAR EN OS

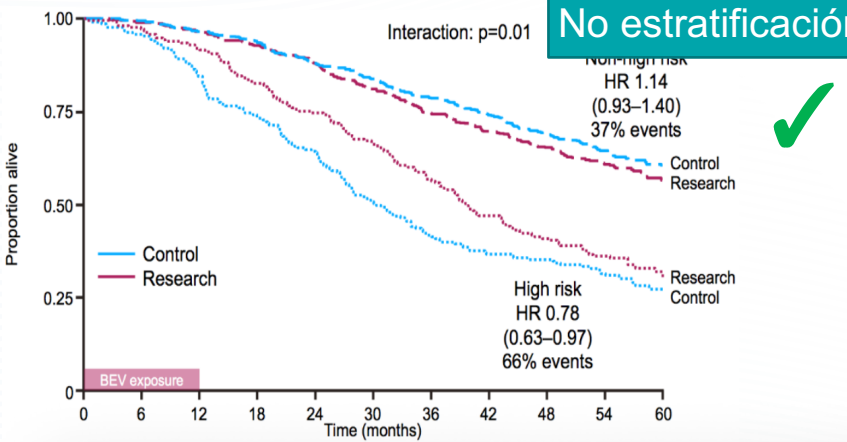
TRATAMIENTOS DE MANTENIMIENTO 1L COA: BEVACIZUMAB

ICON-7

Alto riesgo (30% de toda la población): E. III enf residual > 1 cm / E. IV

	QT (n=254)	QT + Bev (n=248)
Muertos (%)	174	158
Tiempo medio de supervivencia (restringida), meses	34,5	39,3
Mediana, meses	30,2	39,7

HR 0.78

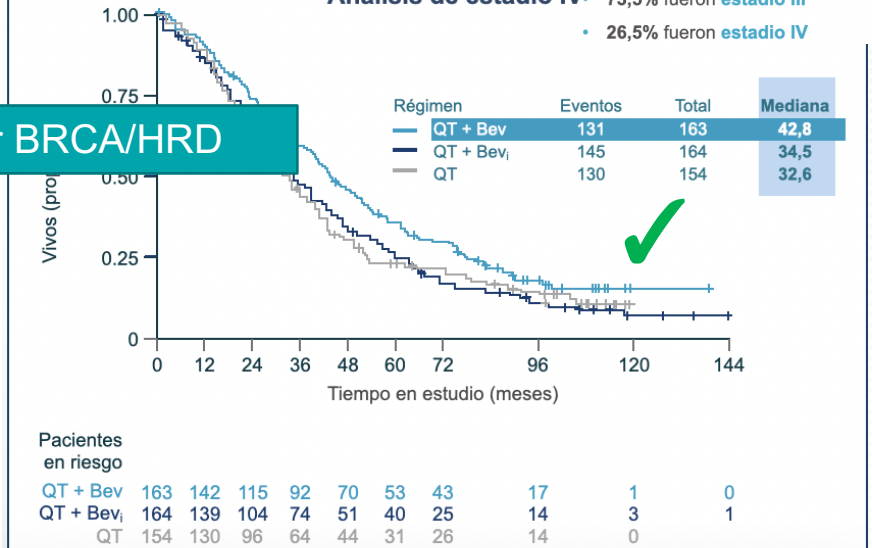


No estratificación por BRCA/HRD

GOG-0218

QT+ Bev mantenimiento

Análisis de estadio IV
- 73,5% fueron estadio III
- 26,5% fueron estadio IV



Tiempo medio de OS (meses) en alto riesgo con Qt + Bv: 39.3 (ICON7) / 42.8 (GOG-0218)

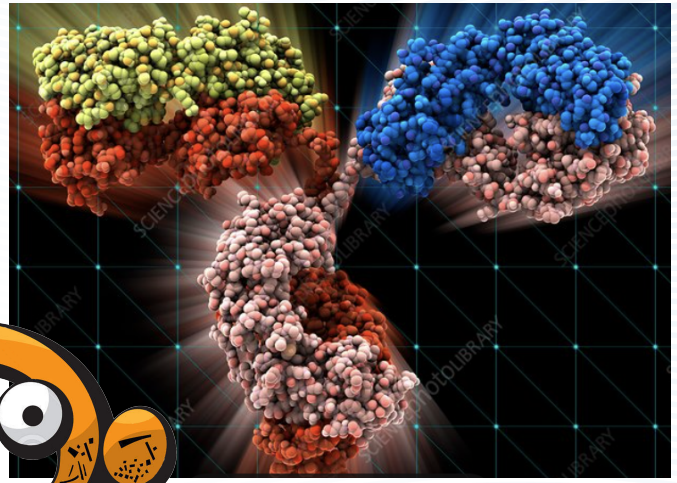
Tiempo medio (meses) de PFS con Qt + Bv: 19.8 (ICON7) / 14.1 (GOG-0218)

1. Oza etc a. ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):928-36. doi: 10.1016/S1470-2045(15)00086-8. Epub 2015 Jun 23.
2. Tewari et al. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. J Clin Oncol. 2019 Sep 10;37(26):2317-2328.

TRATAMIENTOS DE MANTENIMIENTO 1L COA

Un cáncer de ovario HRD+ debería…

- Responder a platino
- Responder a iPARP de mantenimiento
- Beneficiarse de un tratamiento con Bevacizumab

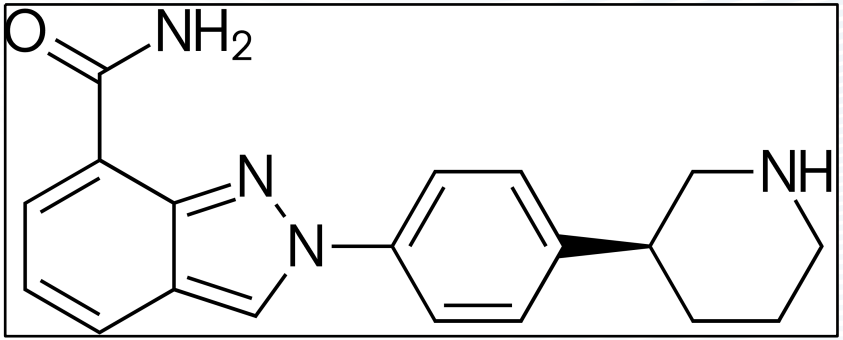


TRATAMIENTOS DE MANTENIMIENTO 1L COA

Tratamientos con Bevacizumab

- ICON 7 / GOG-0218

Tratamientos con iPARP



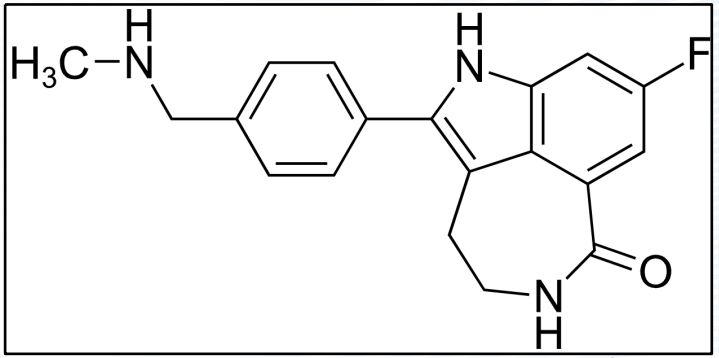
- Niraparib: PRIMA (Niraparib vs placebo de mantenimiento tras respuesta a platino x 3 años)

TRATAMIENTOS DE MANTENIMIENTO 1L COA

Tratamientos con Bevacizumab

- ICON 7 / GOG-0218

Tratamientos con iPARP



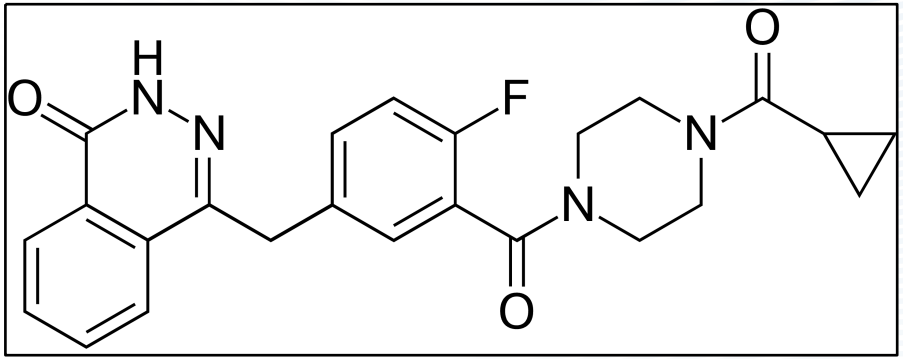
- Niraparib: PRIMA (Niraparib vs placebo de mantenimiento tras respuesta a platino x 3 años)
- Rucaparib: ATHENA-MONO (Rucaparib vs placebo de mantenimiento tras respuesta a platino x 2 años)

TRATAMIENTOS DE MANTENIMIENTO 1L COA

Tratamientos con Bevacizumab

- ICON 7 / GOG-0218

Tratamientos con iPARP



- Niraparib: PRIMA (Niraparib vs placebo de mantenimiento tras respuesta a platino x 3 años)
- Rucaparib: ATHENA-MONO (Rucaparib vs placebo de mantenimiento tras respuesta a platino x 2 años)
- Olaparib:
    - SOLO-1: Olaparib vs placebo de mantenimiento tras respuesta a platino x 2 años
    - PAOLA-1: Olaparib (x 2 años)-Bevacizumab (x 15 meses) vs Bevacizumab x 15 meses de mantenimiento tras respuesta a platino

TRATAMIENTOS DE MANTENIMIENTO 1L COA

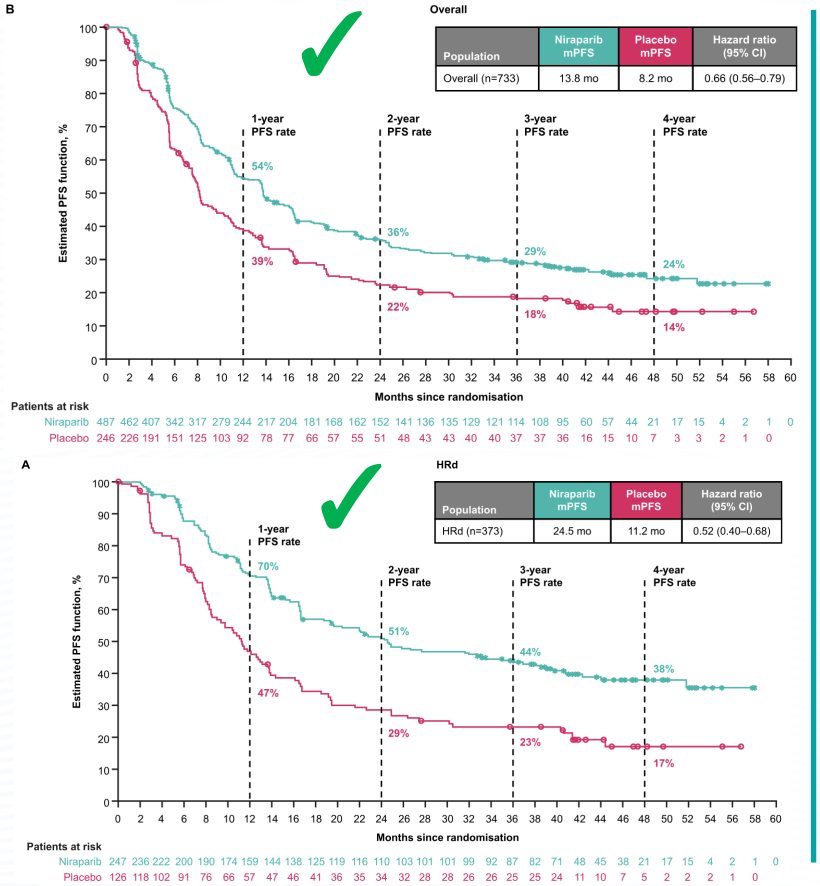
Características comunes ensayos iPARP +/- BV

- Toda la población a estudio y estratificado para HRD/BRCA (SOLO-1*)
- Ca. Epitelial de alto grado de ovario, trompa de falopio o primario peritoneal
- Estadios III y IV
- Mismo endpoint 1º (PFS) y 2º (PFS2, OS, TFST, TSST, seguridad, QoL…)
- **Demostrar platino-sensibilidad***

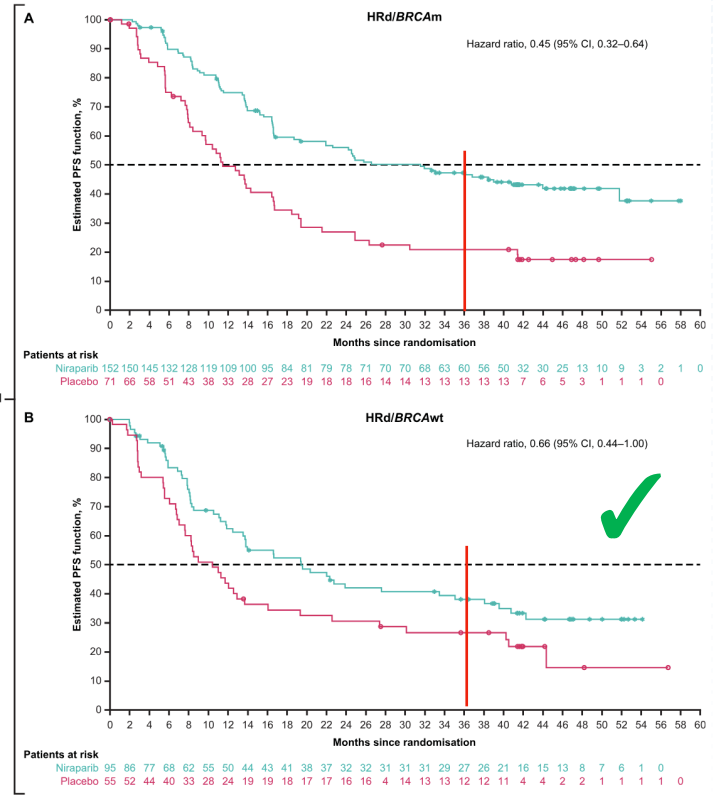
NIRAPARIB. PRIMA PFS (3.5 años)

Original Research

Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer

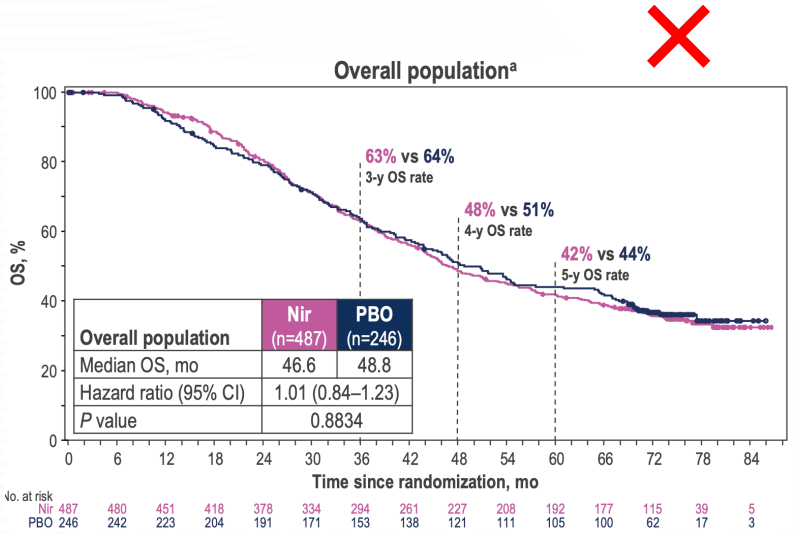


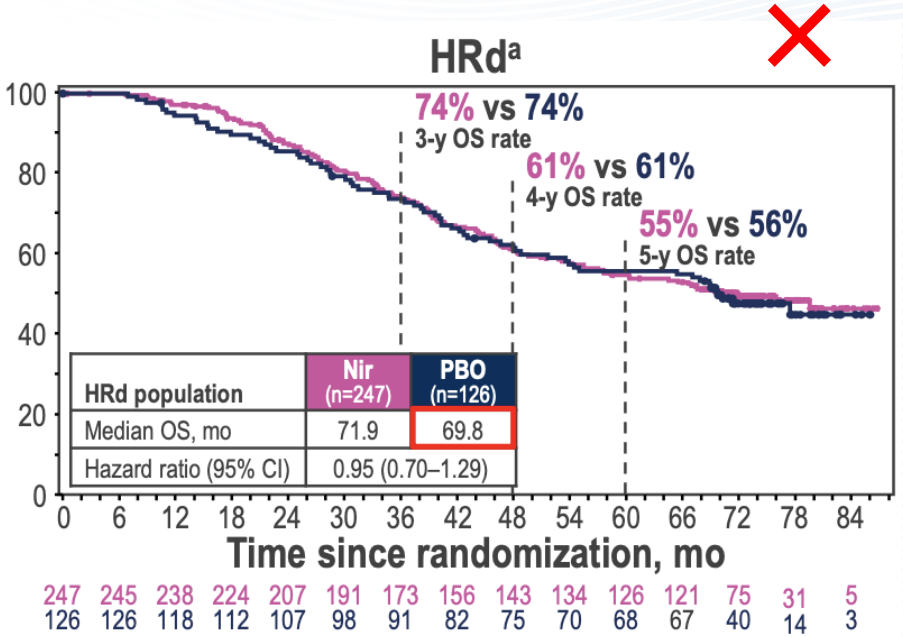
HRd



NIRAPARIB. PRIMA (OS)

Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial☆

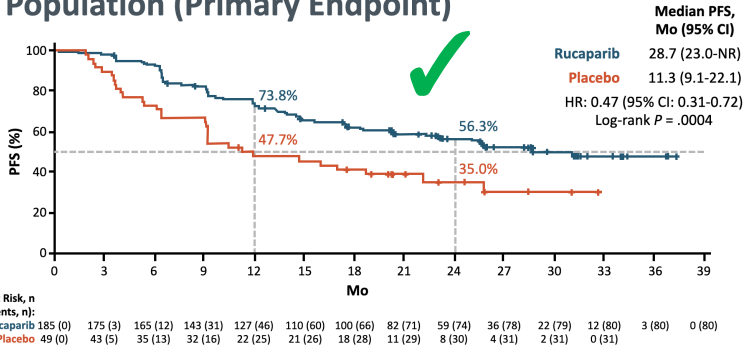




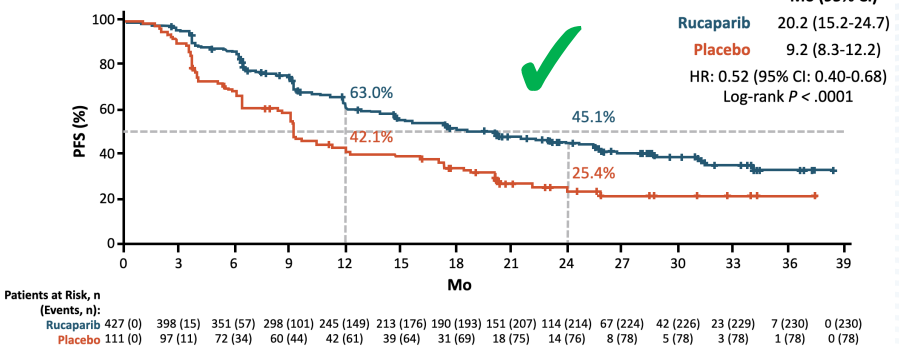
González-Martín A, et al. presented at ESMO 2024 13 -17 September, Barcelona

RUCAPARIB. ATHENA-MONO (PFS)

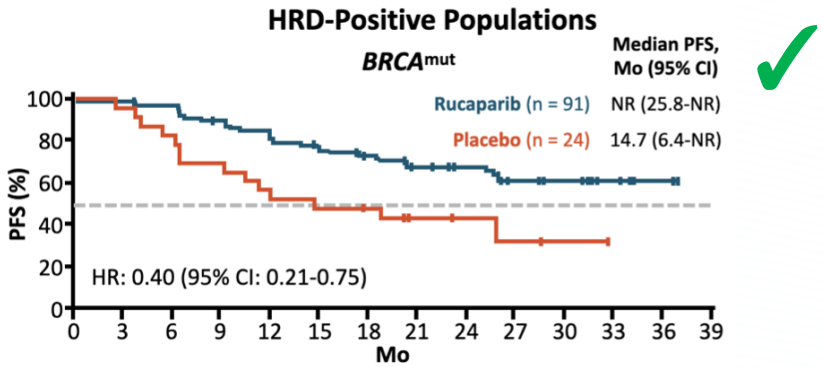
HRD Population (Primary Endpoint)

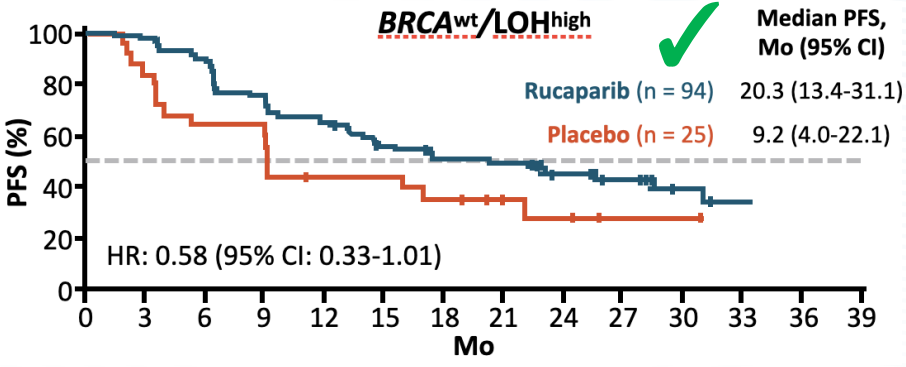


ITT Population (Primary Endpoint)



HRD-Positive Populations



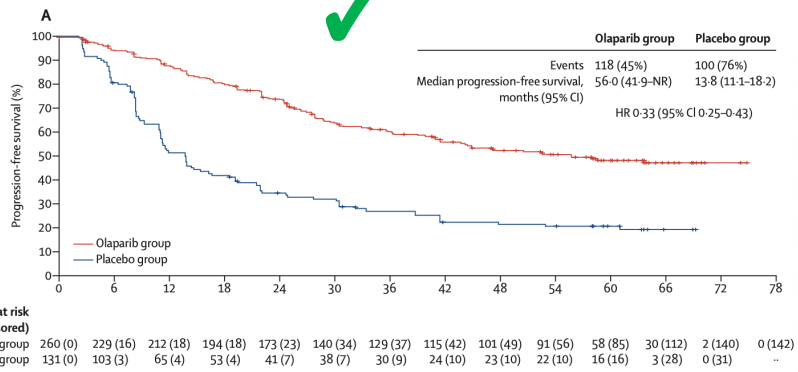


Monk. ASCO 2022. Abstr LBA5500. Monk. JCO. 2022;[Epub].

Población BRCA exclusivamente

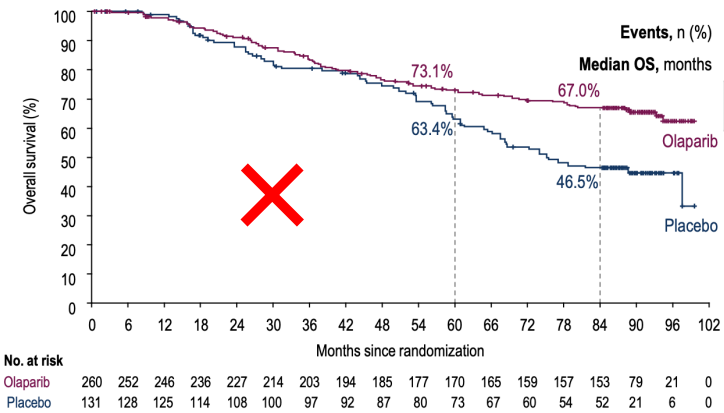
Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a *BRCA* mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial

Susana Banerjee, Kathleen N Moore, Nicoletta Colombo, Giovanni Scambia, Byoung-Gie Kim, Ana Oaknin, Michael Friedlander, Alla Lisyanskaya, Anne Floquet, Alexandra Leary, Gabe S Sonke, Charlie Gourley, Amit Oza, Antonio González-Martín, Carol Aghajanian, William H Bradley, Eileen Holmes, Elizabeth S Lowe, Paul DiSilvestro



Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial

Paul DiSilvestro, MD[1]; Susana Banerjee, MD, PhD[2]; Nicoletta Colombo, MD, PhD[3]; Giovanni Scambia, MD[4]; Byoung-Gie Kim, MD, PhD[5]; Ana Oaknin, MD, PhD[6]; Michael Friedlander, MD[7]; Alla Lisyanskaya, MD[8]; Anne Floquet, MD[9,10]; Alexandra Leary, MD[10,11]; Gabe S. Sonke, MD, PhD[12]; Charlie Gourley, MD, PhD[13]; Amit Oza, MD[14]; Antonio González-Martín, MD, PhD[15,16]; Carol Aghajanian, MD[17]; William Bradley, MD[18]; Cara Mathews, MD[1]; Joyce Liu, MD[19]; John McNamara, MSc[20]; Elizabeth S. Lowe, MD[21]; Mei-Lin Ah-See, MB BChir, MD[22]; and Kathleen N. Moore, MD[23]; on behalf of the SOLO1 Investigators



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

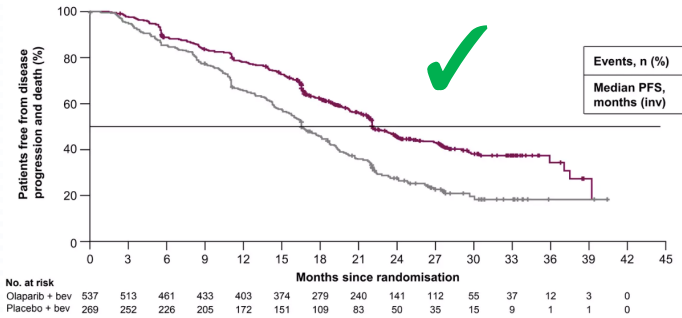
HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

*$P<0.0001$ required to declare statistical significance

OLAPARIB. PAOLA-1 (PFS a 5 años)

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

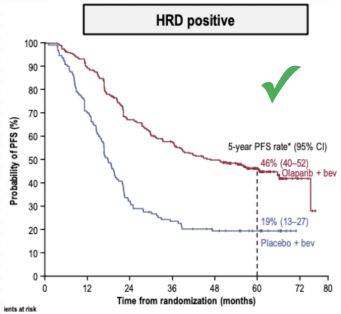
PFS by BICR was consistent with investigator-assessed PFS, indicating robustness of the result



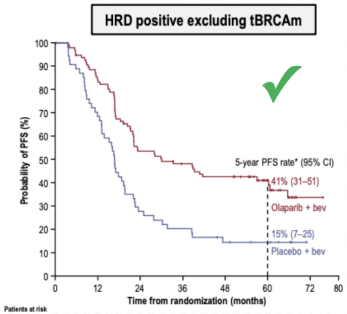
	Olaparib + bevacizumab n=537	Placebo + bevacizumab n=269
Events, n (%)	280 (52)	194 (72)
Median PFS, months (inv)	22.1	16.6
	HR 0.59 95% CI 0.49–0.72 p<0.001	

Primary endpoint: investigator-assessed PFS

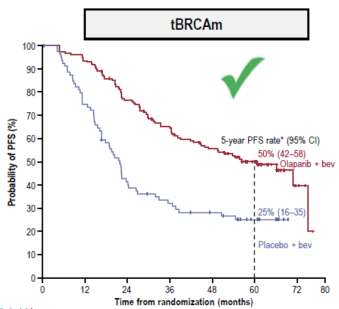
Median time from first cycle of chemotherapy to randomisation = **7 months**[2]



	Olaparib + bev (N=255)	Placebo + bev (N=132)
Events, n (%)	136 (53)	104 (79)
Median PFS, months	46.8	17.6
HR (95% CI)	**0.41** (0.32–0.54)	



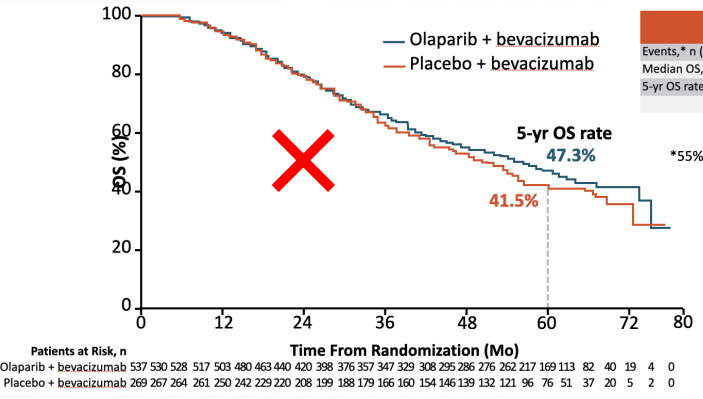
	Olaparib + bev (N=97)	Placebo + bev (N=55)
Events, n (%)	58 (60)	46 (84)
Median PFS, months	30.0	16.6
HR (95% CI)	**0.47** (0.32–0.70)	



	Olaparib + bev (N=157)	Placebo + bev (N=80)
Events, n (%)	78 (50)	58 (73)
Median PFS, months	60.7	21.7
HR (95% CI)	**0.45** (0.32–0.64)	

Ray-Coquard et al. N Engl J Med. 2019 Dec 19;381(25):2416-2428

Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial

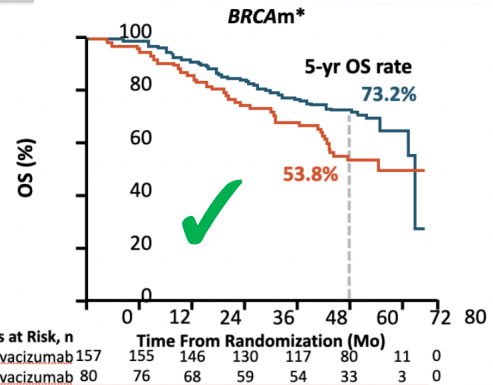


	Olaparib + Bev (n = 537)	Placebo + Bev (n = 269)
Events,* n (%)	288 (53.6)	158 (58.7)
Median OS, mo	56.5	51.6
5-yr OS rate, %	47.3	41.5
HR: 0.92 (95% CI: 0.76-1.12		

*55% maturity.

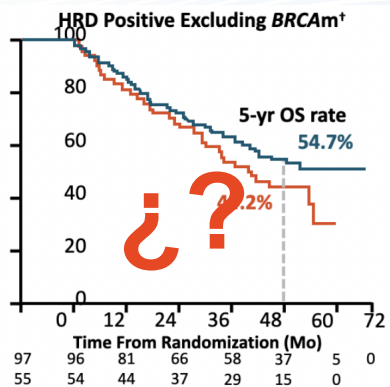
HR 0.92 (0.76-1.12)

HR 0.60 (0.39-0.93)



	Olaparib + Bev (n = 157)	Placebo + Bev (n = 80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, mo	75.2†	66.9
5-yr OS rate, %	73.2	53.8
Subsequent PARPi, n (%)	38 (24.2)	44 (55.0)
HR: 0.60 (95% CI: 0.39-0.93)		

HR 0.71 (0.45-1.13)



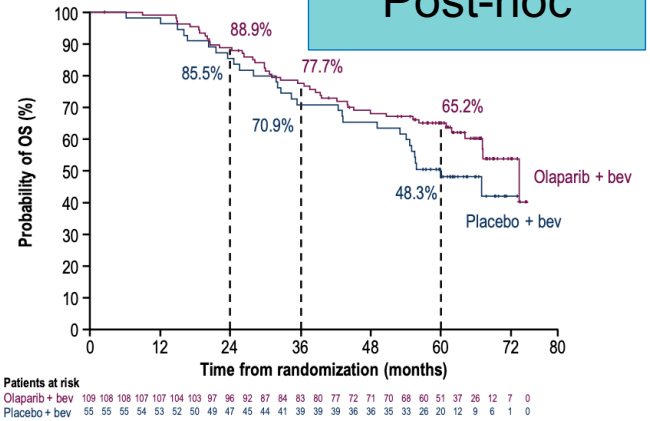
	Olaparib + Bev (n = 97)	Placebo + Bev (n = 55)
Events, n (%)	44 (45.4)	32 (58.2)
Median OS, mo	NR	52.0
5-yr OS rate, %	54.7	44.2
Subsequent PARPi, n (%)	9 (9.3)	23 (41.8)
HR: 0.71 (95% CI: 0.45-1.13)		

Ray-Coquard et al. Ann Oncol. 2023 Aug;34(8):681-692

OLAPARIB. PAOLA-1 (OS SEGÚN RIESGO CLÍNICO)

Post-hoc

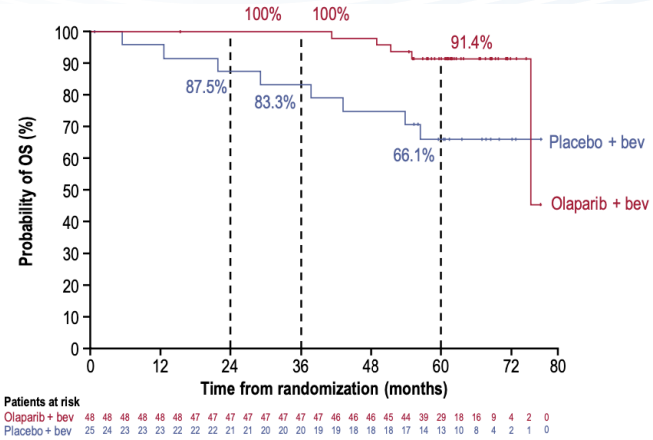
Higher risk



tBRCAm

	Olaparib + bevacizumab (n=109)	Placebo + bevacizumab (n=55)
Events, n (%)	43 (39.4)	29 (52.7)
Median OS, months	73.3*	59.8
5-year OS rate, %	65.2	48.3
	HR 0.69 (95% CI 0.43–1.12)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	25.7	63.6

Lower risk

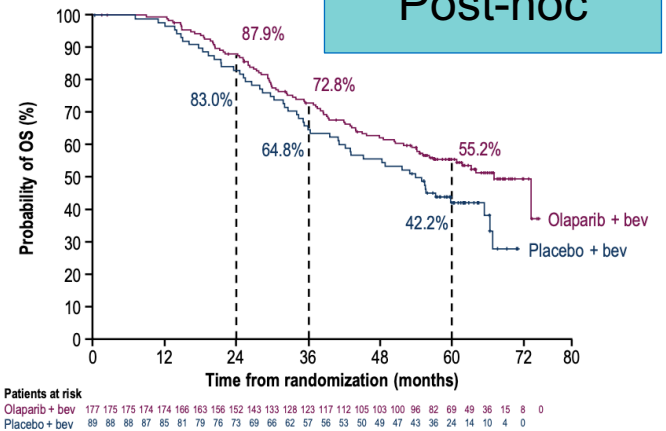


	Olaparib + bevacizumab (n=48)	Placebo + bevacizumab (n=25)
Events, n (%)	5 (10.4)	8 (32.0)
Median OS, months	75.2*	NE
5-year OS rate, %	91.4	66.1
	HR 0.27 (95% CI 0.08–0.80)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	20.8	36.0

OLAPARIB. PAOLA-1 (OS SEGÚN RIESGO CLÍNICO)

Post-hoc

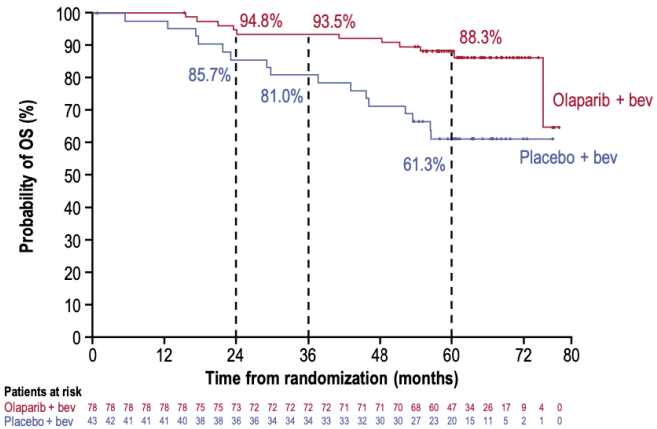
Higher risk



HRD+

	Olaparib + bevacizumab (n=177)	Placebo + bevacizumab (n=89)
Events, n (%)	82 (46.3)	53 (59.6)
Median OS, months	67.0*	54.0
5-year OS rate, %	55.2	42.2
	HR 0.70 (95% CI 0.50–1.00)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	18.6	56.2

Lower risk



	Olaparib + bevacizumab (n=78)	Placebo + bevacizumab (n=43)
Events, n (%)	11 (14.1)	16 (37.2)
Median OS, months	NE	NE
5-year OS rate, %	88.3	61.3
	HR 0.31 (95% CI 0.14–0.66)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	14.1	39.5

BEVACIZUMAB: ¿ES NECESARIO o ES PRESCINDIBLE?

Objetivo del tratamiento de mantenimiento:

- ¿Aumentar PFS + OS?

	PRIMA	ATHENA-MONO	SOLO-1	PAOLA-1
PFS	✓	✓	✓	✓
OS	✗	✗	¿?	✗

A PESAR DE HABER CONSEGUIDO SU ENDPOINT 1º, FDA NO APRUEBA BEVACIZUMAB POR NO IMPACTAR EN OS

- ¿Aumentar PFS + QoL?
- ¿Aumentar PFS + intervalo libre de platino?
- ¿Aumentar PFS + intervalo libre de quimioterapia?

SESG
-Cross
-Recha
-Impac
-% oligoprogresiones candidatas a tto radical
-Nº de líneas de Qt posteriores

BEVACIZUMAB: ¿ES NECESARIO o ES PRESCINDIBLE?

Objetivo del tratamiento de mantenimiento:

- ¿Aumentar PFS + OS?

	PRIMA	ATHENA-MONO	SOLO-1	PAOLA-1
PFS	✓	✓	✓	✓
OS	✗	✗	¿?	✓

PAOLA-1 aumenta OS:

-Por subgrupos moleculares (BRCA/HRD/HRP):

BRCAmut

-Por grupos de riesgo (clínicos)

-HRD+ alto riesgo*

-BRCAmut de bajo riesgo (pocos eventos)

-HRD+ bajo riesgo (pocos eventos)

PAOLA-1: LO QUE NOS CUENTAN vs. LO QUE ES

Hierarchical testing procedure in the ITT[3-5]

PFS ✓ — **Primary endpoint,** tested at the 2-sided p<0.05

→ - BRCAmut/HRD+
- BRCAwt/HRD+
- HRP

Ensayo jerarquizado

If statistically significant

PFS2 ✓ — Final PFS2 at ~ 53% maturity (~411 events) or after a maximum duration of 1 year following the PFS an

→ - BRCAmut/HRD+
- BRCAwt/HRD+
- HRP

If statistically significant

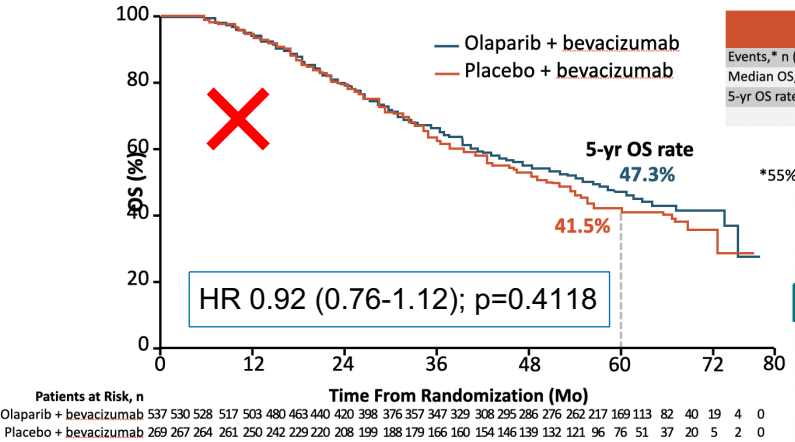
OS ✗ — Final OS analysis ~60% maturity or after a 3-year duration from the main PFS analysis, whichever occu

→ - BRCAmut/HRD+
- BRCAwt/HRD+
- HRP

Ray-Coquard et al. Ann Oncol. 2023 Aug;34(8):681-692

PAOLA-1: LO QUE NOS CUENTAN vs. LO QUE ES

Ensayo jerarquizado



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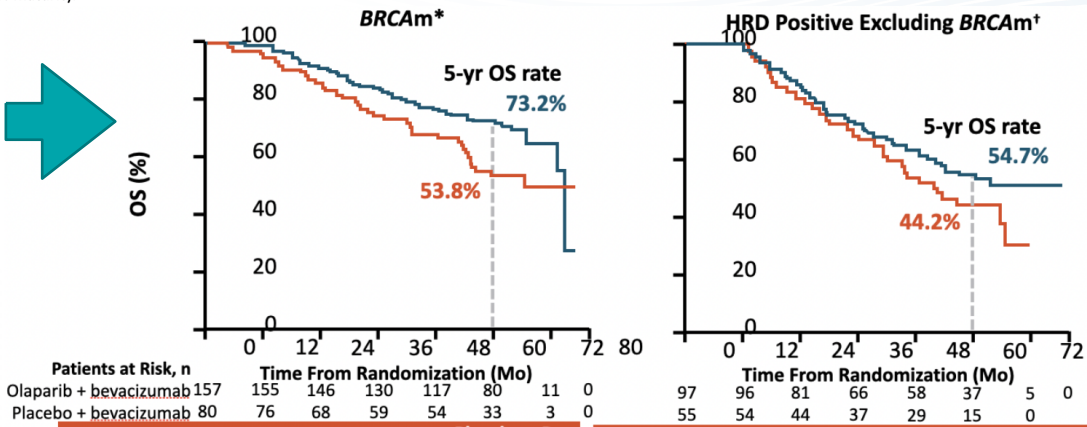
5-yr OS rate, %	47.3	41.5
HR: 0.92 (95% CI: 0.76-1.12; *P* = .4118)		

*55% maturity.

Madurez <50%. Mediana inestable

Madurez definitiva: 55%



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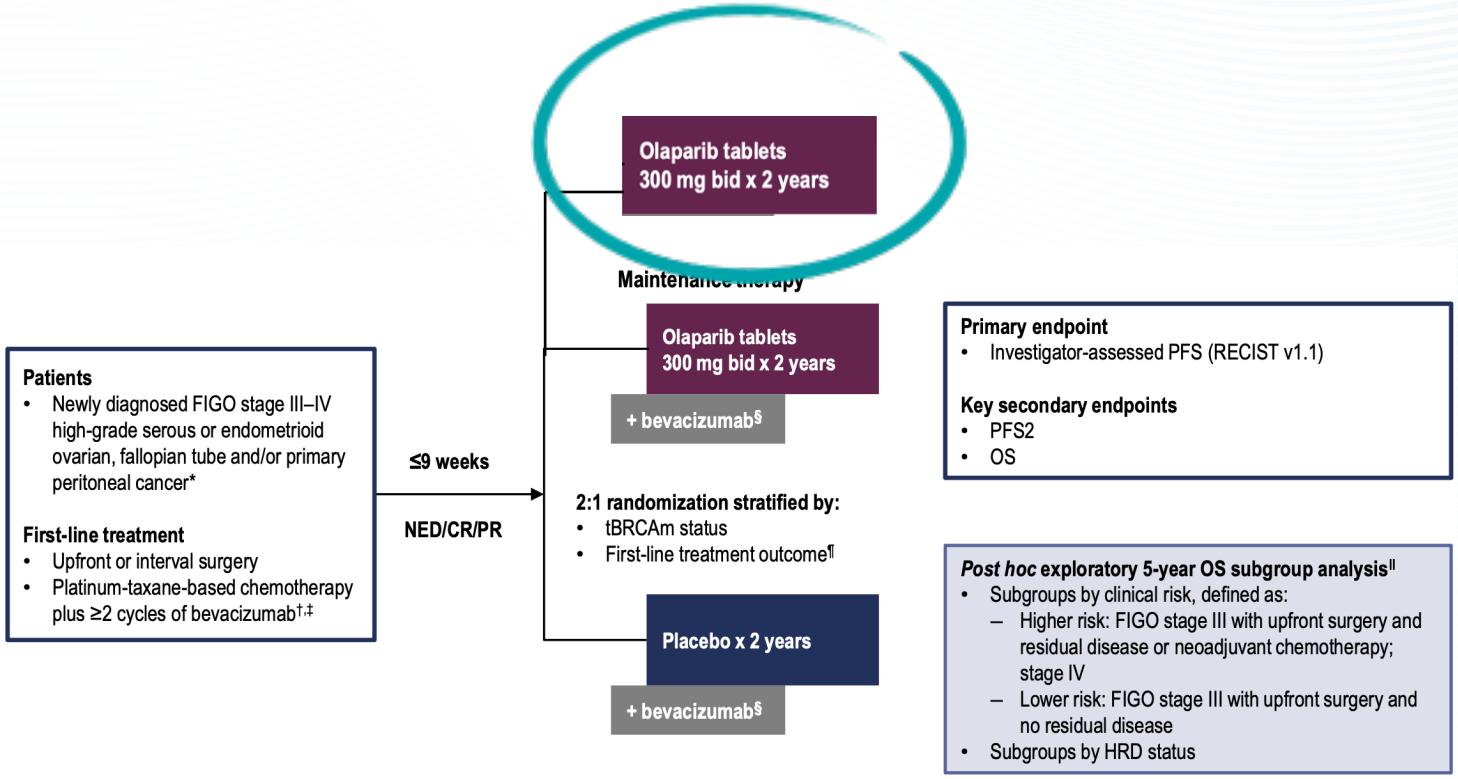
HR: 0.71 (95% CI: 0.45-1.13)		

Generadores de hipótesis

Ray-Coquard et al. Ann Oncol. 2023 Aug;34(8):681-692

PAOLA-1: SI EL ENSAYO HUBIERA TENIDO 3 BRAZOS



Ray-Coquard et al. Ann Oncol. 2023 Aug;34(8):681-692

PAOLA-1, PRIMA y ATHENA-MONO **aumentan PFS (mantenido en HRD+) SIN IMPACTO en OS**

En pacientes HRD+ **iPARP en monoterapia o en combinación con Bevacizumab son opciones válidas**

ASCO Special Articles

Check for updates

Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: ASCO Guideline Update

Clinical Interpretation

In patients with response to platinum-based therapy, options after adjuvant chemotherapy include observation as well as maintenance treatments, and the decision on which option to choose is based on individual patient factors, such as *BRCA* status, HRD test results, stage, extent of response to platinum-based therapy, and patient preference. If bevacizumab was started with chemotherapy, the continuation of bevacizumab for up to 12 months or progression is reasonable. In patients with a germline/somatic *BRCA* pathogenic variants or whose cancer is HRD score positive, PARPi (olaparib and niraparib) are strongly recommended. Tumor testing for somatic pathogenic variants and HRD score should be prioritized with ICS

J Clin Oncol 43:868-891. January 2025

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

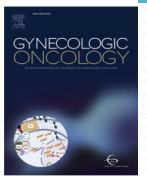
Argumentos a favor de BV

Argumentos en contra de BV

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Review Article

Rationale for combination PARP inhibitor and antiangiogenic treatment in advanced epithelial ovarian cancer: A review

Angeles Alvarez Secord [a,*], David M. O'Malley [b], Anil K. Sood [c], Shannon N. Westin [c], Joyce F. Liu [d]

[a] Division of Gynecology Oncology, Department of Obstetrics and Gynecology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, United States
[b] Division of Gynecology Oncology, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH, United States
[c] Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[d] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States

Hipoxia inducida por antiangiogénicos –> Down-regulación de vía HR –> Mayor dependencia de vías de reparación mediadas por PARP

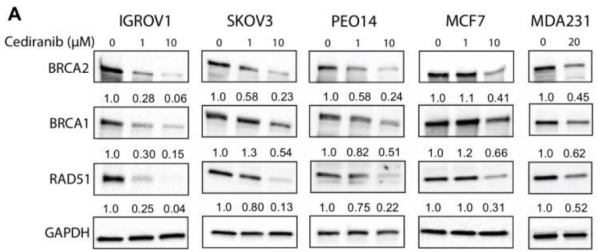
Normalización vascular: optimiza llegada de iPARP a células cancerosas

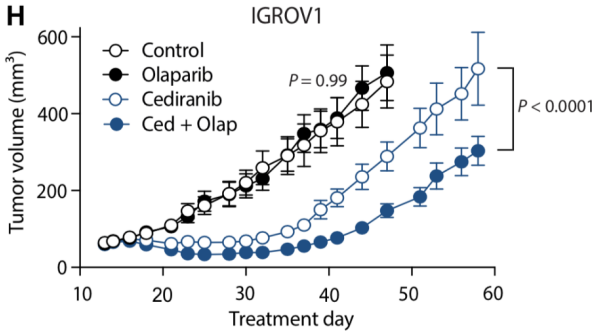
PARP inhibition and angiogenesis

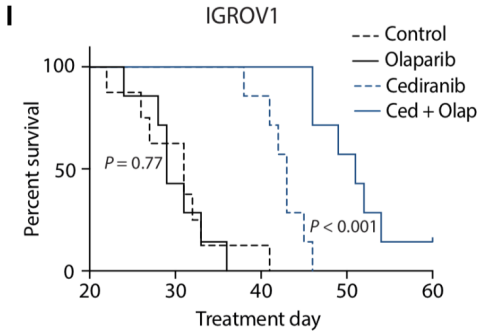
CANCER

Cediranib suppresses homology-directed DNA repair through down-regulation of BRCA1/2 and RAD51

Alanna R. Kaplan[1,2], Susan E. Gueble[1,2], Yanfeng Liu[1], Sebastian Oeck[1], Hoon Kim[1], Zhong Yun[1], Peter M. Glazer[1,3]*







Kaplan et al Sci. Trans. Med (2019) 11:eaav4508

ESMO GYNAECOLOGICAL CANCERS Iain McNeish

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

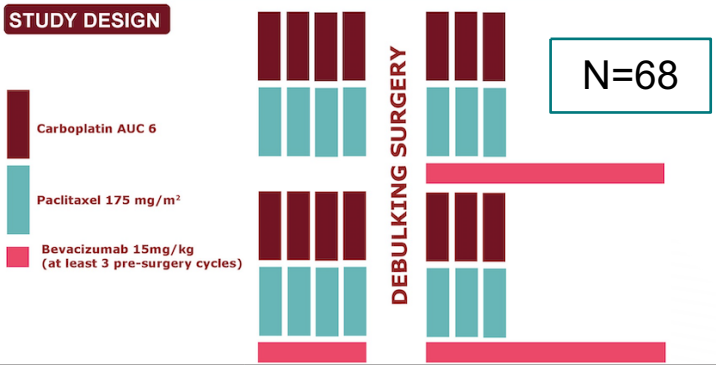
- Efecto sinérgico con iPARP

Argumentos en contra de BV

BEVACIZUMAB EN ALTO RIESGO: beneficio en E. IV, E. III R2… ¿y en la cirugía de intervalo?

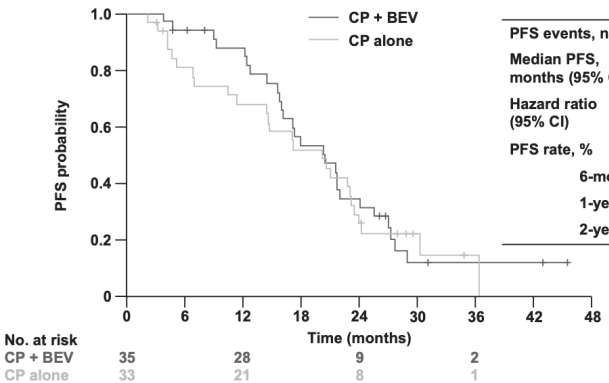
Bevacizumab en alto riesgo: neoadyuvancia

GEICO-1205/NOVA



N=68

Characteristic		CP alone (n=33)	CP + BEV (n=35)
Median age, years (range)		57 (36–82)	63 (33–78)
ECOG PS, n (%)	0	5 (15)	8 (23)
	1	21 (64)	24 (69)
	2	7 (21)	3 (9)
Origin of cancer, n (%)	Ovary	25 (76)	31 (89)
	Primary peritoneal	7 (21)	4 (11)
	Fallopian tube	1 (3)	0
FIGO stage, n (%)	IIIC	22 (67)	23 (66)
	IV	11 (33)	12 (34)
Histological sub-type, n (%)	Serous	26 (79)	27 (77)
	Adenocarcinoma	5 (15)	7 (20)
	Endometrioid/other	2 (6)	1 (3)
Histological grade, n (%)	Grade 3 (poorly differentiated)	32 (97)	35 (100)
	Missing	1 (3)	0



	CP alone (n = 33)	CP + BEV (n = 35)
PFS events, n (%)	26 (79)	27 (77)
Median PFS, months (95% CI)	20.1 (14.7–25.6)	20.4 (14.4–26.3)
Hazard ratio (95% CI)	1.13 (0.66–1.93) Log-rank *P* = 0.664	
PFS rate, %		
6-month	81	94
1-year	68	88
2-year	26	35

¿¿% pacientes HRD+??

- >% de IQ en grupo BV vs QT (89% vs. 67%); p=0.029
- NO diferencias en tasas de respuesta completa macroscópica
- NO diferencias en % de citorreducción completa
- NO diferencias en PFS

Int J Gynecol Cancer. 2019 Jul;29(6):1050-1056.

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

- Efecto sinérgico con iPARP

Argumentos en contra de BV

- No beneficio en QT neoadyuvante

¿HAY ESTUDIOS DE BEVACIZUMAB EN HRD +?

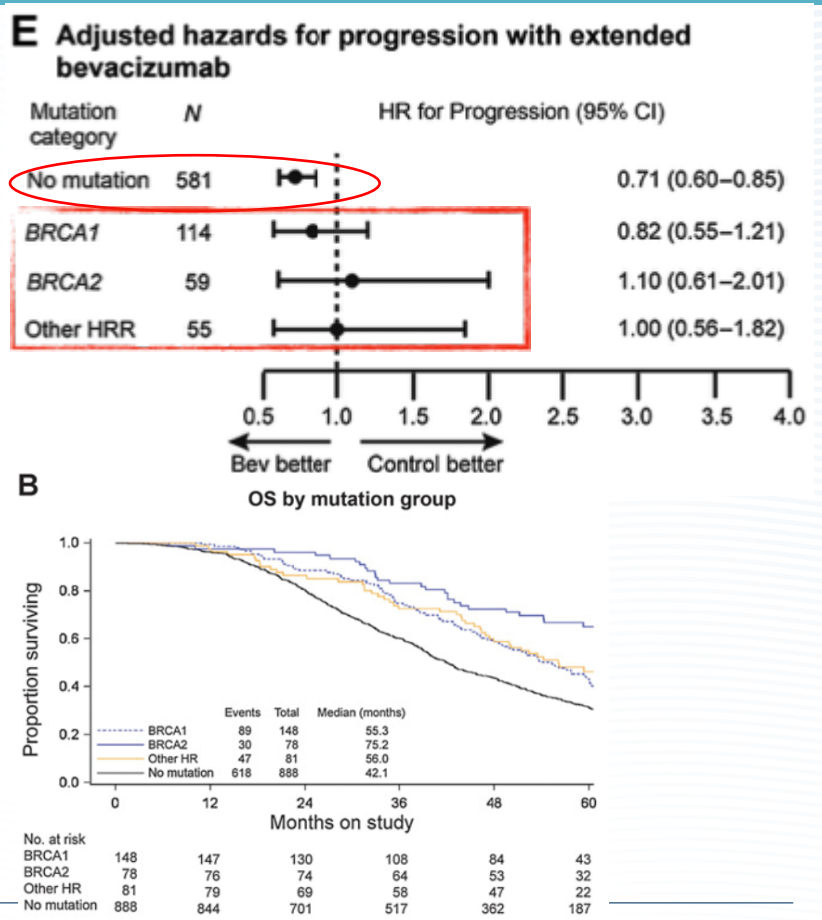
Bevacizumab en HRD +: Estudios retrospectivos

Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study

Barbara M. Norquist[1], Mark F. Brady[2], Maria I. Harrell[1], Tom Walsh[3,4], Ming K. Lee[3,4], Suleyman Gulsuner[3,4], Sarah S. Bernards[1], Silvia Casadei[3,4], Robert A. Burger[5], Krishnansu S. Tewari[6], Floor Backes[7], Robert S. Mannel[8], Gretchen Glaser[9], Cheryl Bailey[10], Stephen Rubin[11], John Soper[12], Heather A. Lankes[13], Nilsa C. Ramirez[13], Mary Claire King[3,4], Michael J. Birrer[14], and Elizabeth M. Swisher[1,3]

De un total de 1195 pacientes, 307 HRD+:
- 148 (12.4%) BRCA1mut
- 78 (6.5%) BRCA2mut
- 81 (6.8%) HRD+/BRCAwt

Comparados con el subgrupo de no-mutados:
- Viven más los HRD+ (PFS/OS)
- BV NO impacta en PFS/OS en este grupo



Norquist et al. Clin Cancer Res. 2018 Feb 15;24(4):777-783.

Bevacizumab as maintenance treatment in BRCA mutated patients with advanced ovarian cancer: A large, retrospective, multicenter case-control study

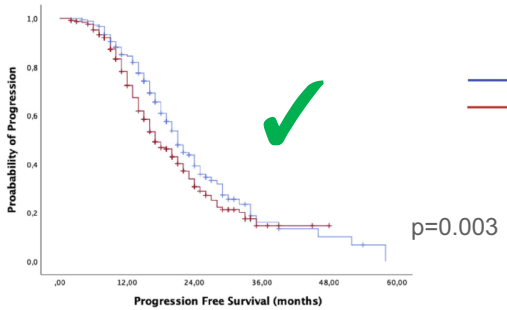
D. Lorusso [a,1], C. Marchetti [a,1], C. Conte [a,b], E. Giudice [b], G. Bolomini [a], L. Vertechy [a], V. Ceni [c], A. Ditto [d], G. Ferrandina [a,b], F. Raspagliesi [d], G. Scambia [a,b,*], A. Fagotti [a,b]

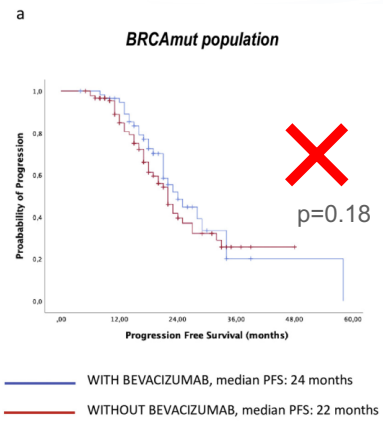
- Enero/2015- Junio/2019
- 1ª Línea CBDCA-Taxol semanal +/-Bv
- Estatus BRCA conocido

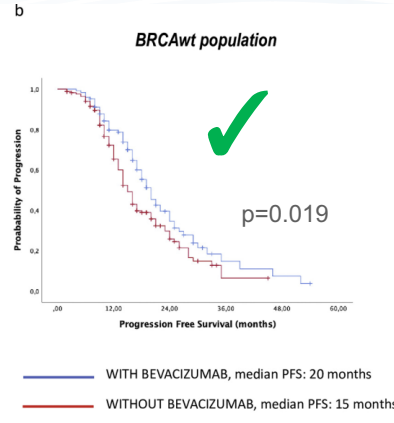
n= 441 (183 Bv vs. 258 no mantenimiento)
Mutaciones BRCA: 148 (58 recibieron Bv)

Cox univariate and multivariate analysis for OS.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.02 (1.00–1.04)	0.04	1.00 (0.98–1.02)	0.53
ECOG 0/≥1	1.18 (0.74–1.90)	0.46		
BRCAmut/BRCAwt status	0.35 (0.20–0.61)	0.0001	0.34 (0.19–0.61)	0.0001
PDS/NACT	0.49 (0.31–0.77)	0.002	0.52 (0.32–0.86)	0.01
RT 0/>0	0.68 (0.38–1.19)	0.17		
Bevacizumab yes/no	0.34 (0.64–1.00)	0.053	0.82 (0.50–1.36)	0.46







¿Aporta algo el Bevacizumab en pacientes HRD +?

Argumentos a favor de BV

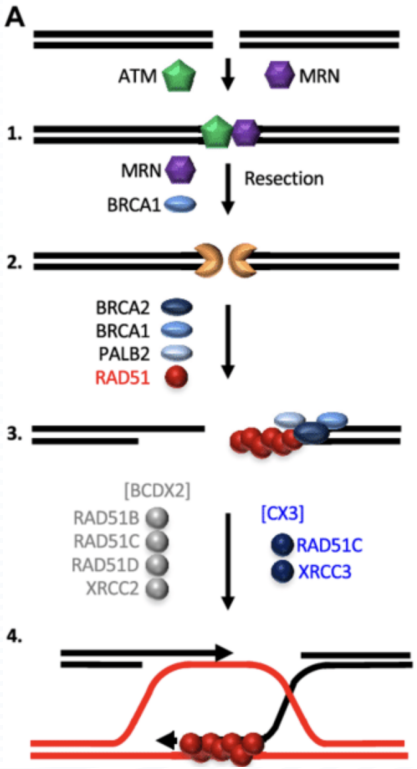
- Efecto sinérgico con iPARP

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut

HRD + COMO BIOMARCADOR: ¿Todas las mutaciones en genes de HR responden a iPARP?

HRD + como biomarcador predictivo de respuesta: ¿Todos los HRD+ responden a iPARP?



B

Gene	Relationship with HR
BRCA1	Favours resection; favours the loading of RAD51
BRCA2	Loads RAD51 on the ssDNA
PALB2	Loads RAD51 on the ssDNA
RAD51C	Paralog of RAD51; favours the loading of RAD51, stabilizes the ssDNA/RAD51 filament, extends the intermediates
RAD51D	Paralog of RAD51; favours the loading of RAD51, stabilizes the ssDNA/RAD51 filament, extends the intermediates
BARD1	Interactor of BRCA1
BRIP1	Paralog of RAD51; favours the loading of RAD51, stabilizes the ssDNA/RAD51 filament, extends the intermediates
MRE11	Member of the MRN complex; signalling of the DSB; initiation of the resection
RAD50	Member of the MRN complex; signalling of the DSB; initiation of the resection
NBN	Member of the MRN complex; signalling of the DSB; initiation of the resection
ATM	Signalling of the DSB
CHEK2	Signalling of the DSB
TP53	Controls cell cycle checkpoint, apoptosis and senescence; inhibits HR
PTEN	Antagonist of AKT1; impacts HR genes expression
NF1	*(Neurofibromatosis type 1)*
CDH1	*(Hereditary Diffuse Gastric Cancer)*
STK11	*(Peutz-Jeghers syndrome)*

2022-RA-466-ESGO

LONG-TERM RESPONDERS (LTR) TO RUCAPARIB IN RECURRENT OVARIAN CANCER: A SUB-GROUP ANALYSIS FROM THE RUCAPARIB ACCESS (RAP) PROGRAM IN SPAIN BY GEICO

Molecular and clinical determinants of response and resistance to rucaparib for recurrent ovarian cancer treatment in ARIEL2 (Parts 1 and 2)

BRCA1, BRCA2, RAD51C y PALB2 predicen eficacia iPARP

***BRIP1* mutation does not confer sensitivity to PARP inhibition**

A. Castaneda[a], C. Moyer[a], J.L. Gillespie[b], R. Doberstein[a], F.J. Backes[a,b], D.E. Cohn[a,b], P.J. Goodfellow[c]. [a]*The Ohio State University, Columbus, OH, USA,* [b]*The Ohio State University, James Cancer Hospital, Columbus, OH, USA,* [c]*The Ohio State University Medical Center, Columbus, OH, USA*

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

- Efecto sinérgico con iPARP
- No toda mutación en HRD responde a iPARP

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut

¿UTILIZAN LOS EC (PRIMA, PAOLA, ATHENA-MONO) EL ESTATUS HRD COMO CRITERIO DE INCLUSIÓN?

NO. UTILIZAN EL CONCEPTO DE “PLATINO-SENSIBILIDAD”

¿CÓMO DEFINIR LA PLATINO-SENSIBILIDAD?

¿CÓMO DEFINIR LA PLATINO-SENSIBILIDAD?

¿Qué es la platino-sensibilidad?

Distintas definiciones

SOLO-1: Partial response: ≥30% decrease in tumor volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range

PAOLA-1: Partial response was defined as radiologic evidence of disease, an abnormal CA-125 level, or both.

PRIMA: Complete or partial tumor response to platinum-based regimen per RECIST criteria, either CA-125 in the normal range or CA-125 decrease by more than 90**%** during their front-line therapy, stable for ≥7 days (no increase >15%)

ATHENA-MONO:complete response or partial response by RECIST v1.1, or a cancer antigen (CA-125) response by Gynecologic Cancer Intergroup criteria in patients with non-measurable disease (>50%)

Moore et al. N Engl J Med. 2018 Dec 27;379(26):2495-2505; Ray-Coquard et al. N Engl J Med. 2019 Dec 19;381(25):2416-2428.
González-Martín et al. N Engl J Med. 2019 Dec 19;381(25):2391-2402; Monk. ASCO 2022. Abstr LBA5500. Monk. JCO. 2022;[Epub].

MEDIR ¿CÓMO ~~DEFINIR~~ LA PLATINO-SENSIBILIDAD?

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ATHENA-MONO:complete response or partial response by RECIST v1.1, or a cancer antigen (CA-125) response by Gynecologic Cancer Intergroup criteria in patients with non-measurable disease (>50%)

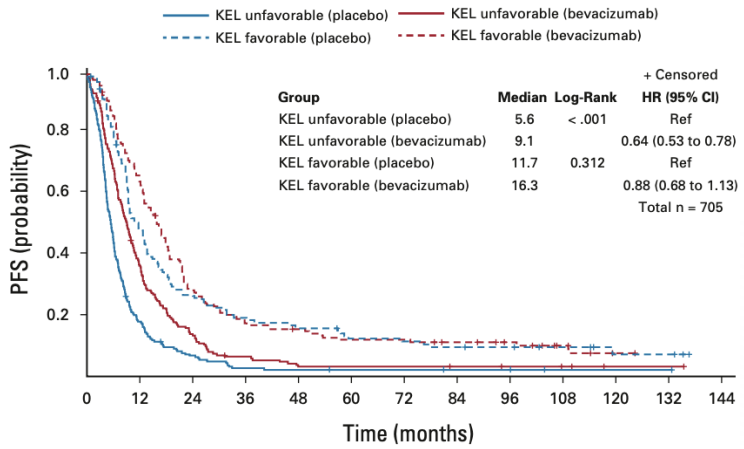
Distintas mediciones

- **Clínica** (ascitis, disnea, suboclusión…)
- **Radiológica**: RECIST
- **Patológica**: CRS
- **Bioquímica**: reducción de Ca125 / **KELIM**

Moore et al. N Engl J Med. 2018 Dec 27;379(26):2495-2505; Ray-Coquard et al. N Engl J Med. 2019 Dec 19;381(25):2416-2428
González-Martín et al. N Engl J Med. 2019 Dec 19;381(25):2391-2402; Monk. ASCO 2022. Abstr LBA5500. Monk. JCO. 2022;[Epub].

KELIM DEFINE BENEFICIO DE 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

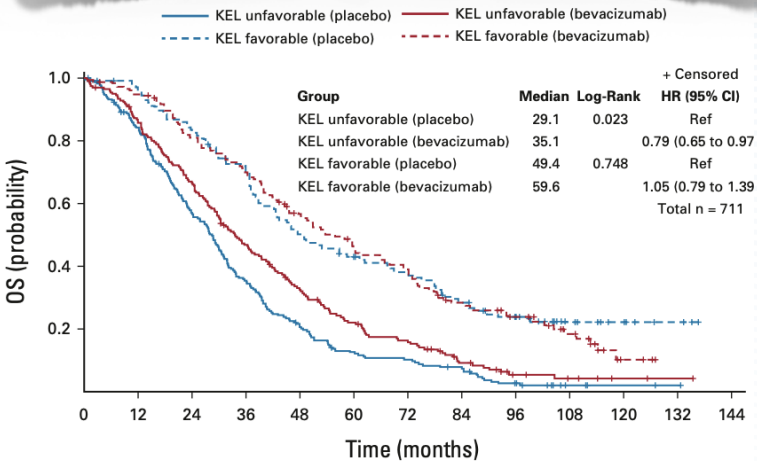


No. at risk:

KEL unfavorable (placebo)	230	6	4	1	0
KEL unfavorable (bevacizumab)	203	12	6	3	0
KEL favorable (placebo)	122	23	13	7	0
KEL favorable (bevacizumab)	150	26	17	4	0

No impacto en PFS (HR, 0.96; 95% CI, 0.79 to 1.17) ni OS (HR, 1.11; 95% CI, 0.89 to 1.39) si KELIM FAVORABLE

IMPACTO EN PFS Y OS EN ALTO RIESGO EN KELIM DESFAVORABLE (NO EN FAVORABLE)



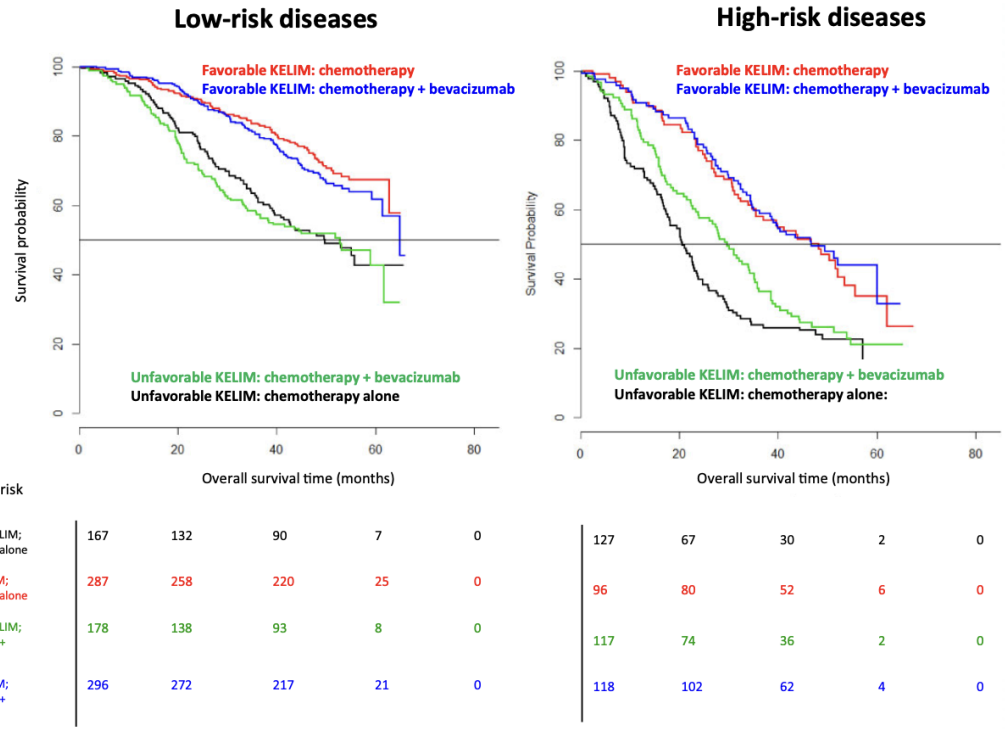
No. at risk:

KEL unfavorable (placebo)	232	87	31	4	0
KEL unfavorable (bevacizumab)	206	98	36	5	0
KEL favorable (placebo)	122	85	45	13	0
KEL favorable (bevacizumab)	151	106	58	16	0

JNCI Cancer Spectrum (2020) 4(3); J Clin Oncol 40:3965-3974

KELIM DEFINE BENEFICIO DE BEVACIZUMAB

Bevacizumab for Newly Diagnosed Ovarian Cancers: Best Candidates Among High-Risk Disease Patients (ICON-7)



En el grupo de alto riesgo…

Los pacientes con **KELIM FAVORABLE no se beneficiaban** (OS) de Bevacizumab (46.6 vs 48.2 meses); p=0.70; HR 0.93 (95% CI 0.65-1.34)

-Los pacientes con **KELIM DESFAVORABLE se beneficiaban, aunque no estadísticamente significativo** (p=0.09; HR 0.78 (95% CI 0.58-1.04)

JNCI Cancer Spectrum (2020) 4(3); J Clin Oncol 40:3965-3974

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

- Efecto sinérgico con iPARP
- No toda mutación en HRD responde a iPARP

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut

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- KELIM desfavorable y alto riesgo

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut
- KELIM favorable

SI iPARP+/-Bv NO IMPACTA EN OS… ¿HAY IMPACTO DE OTROS ENDPOINT SECUNDARIOS?

¿IMPACTO DE OTROS ENDPOINT SECUNDARIOS?

¿Cual es el mejor endpoint subrogado de PFS?

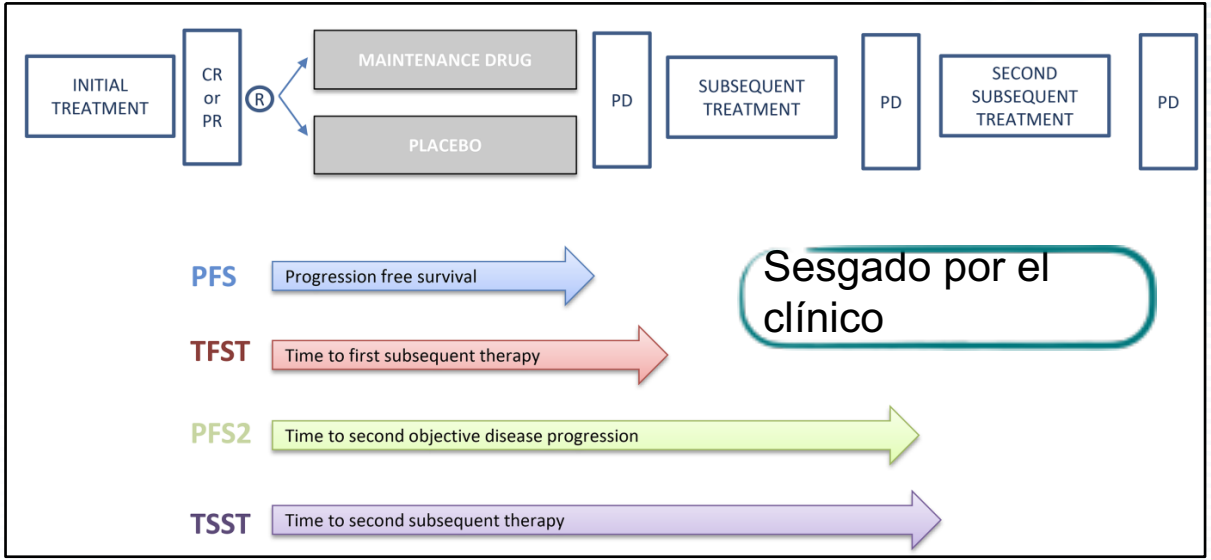
- ¿PFS2?
- ¿TSST?
- ¿QoL?
- ¿Tiempo hasta la platino resistencia?

Outcomes and endpoints of rele
gynecologic cancer clinical tria

Ainhoa Madariaga ,[1] Rodrigo Sanchez-Bayona,[1] Fernanda G He
Antonio González Martín [4]

Other time to event endpoints, including time from randomization to progression on the second-line therapy or death (progression-free survival two) and time to second subsequent therapy, can be used as secondary outcomes in phase III clinical trials (Figure 1).[41] These measures are important to support the hypothesis that the benefit provided by the increase in progression-free survival is maintained over time, and the disease remains controlled at a longer term.[41] In cases where it is not feasible to ensure regular disease reassessment until the time of second progression, time to second subsequent therapy should be used instead of progression-free survival two.

Regulatory agencies recommend that maintenance trials should report the impact in the subsequent line of therapy. Both progression-free survival two and time to second subsequent therapy have an important role in studies assessing maintenance strategies.[41] Prolonged administration of a treatment as maintenance may reduce the ability of patients to benefit from the same or similar agents; patients could develop cross-resistances and treatment-related toxicity that might decrease tolerance to subsequent therapy. Analysis of the benefit in time to second subsequent therapy could help to elucidate whether a statistically non-significant difference in overall survival might be real.[41]



ELSEVIER

Available online at www.sciencedirect.com

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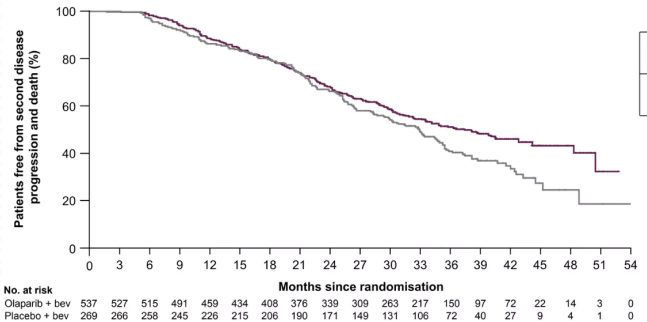
journal homepage: www.ejcancer.com

Original Research

Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial



	Olaparib + bevacizumab n=537	Placebo + bevacizumab n=269
Events, n (%)	260 (48)	164 (61)
Median PFS2, months	36.5	32.6
	HR 0.78 95% CI 0.64–0.95 *P*=0.0125	

27% of patients in the placebo arm and 9% in the olaparib arm received a PARP inhibitor as their first subsequent treatment

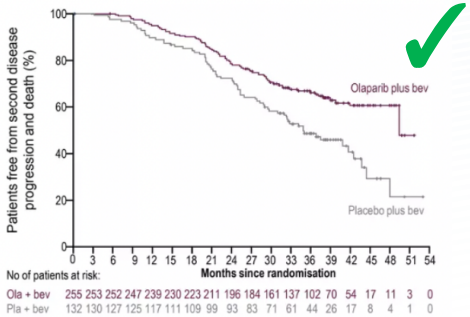
Aumento de PFS2 en:

ITT: HR 0.78 (0.64-0.95; p=0.0125)

HRD+: HR 0.56 (0.41-0.77)

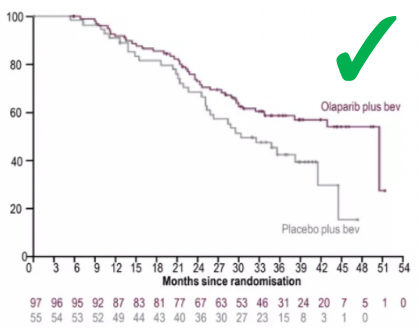
HRD+/BRCAwt: HR 0.6 (0.38-0.96)

HRD-positive,* including tBRCAm



	Olaparib + bevacizumab n=255	Placebo + bevacizumab n=132
Events, n (%)	85 (33)	70 (53)
Median PFS2, months	50.3‡	35.3
	HR 0.56 95% CI 0.41–0.77	

HRD-positive,* excluding tBRCAm



	Olaparib + bevacizumab n=97	Placebo + bevacizumab n=55
41 (42)	33 (60)	
50.3‡	30.1	
	HR 0.60 95% CI 0.38–0.96	

¿IMPACTO DE OTROS ENDPOINT SECUNDARIOS? PFS2. ATHENA-MONO y PRIMA.

ESGO 2025

PSA-063 ATHENA-MONO Post-Progression Survival Data Update in Patients With Newly Diagnosed Advanced Ovarian Cancer

Sharad Ghamande, Rowan E. Miller, Ekaterina Solovyeva, Emily Prendergast, Maria Del Mar Gordon Santiago, Yong-Man Kim, Ramey Littell, Nuria Ruiz, Paul Bessette

Endpoint	HR (95% CI)
PFS2 (Progression-Free Survival 2)	0.74 [0.47-1.17]
TFST (Time to First Subsequent Therapy)	0.66 [0.37-0.82]
TSST (Time to Second Subsequent Therapy)	0.89 [0.43-1.09]

PRIMA

Prespecified secondary efficacy endpoint	Overall population		All HRd		HRd/*BRCA*m		HRd/*BRCA*wt	
	Niraparib (*n* = 487)	Placebo (*n* = 246)	Niraparib (*n* = 247)	Placebo (*n* = 126)	Niraparib (*n* = 152)	Placebo (*n* = 71)	Niraparib (*n* = 94)	Placebo (*n* = 55)
TFST								
Median, months	17.0	12.0	26.9	13.9	34.3	14.9	22.5	12.9
Hazard ratio, 95% CI	0.74 (0.62-0.89)		0.55 (0.43-0.71)		0.45 (0.32-0.62)		0.76 (0.50-1.14)	
PFS2								
Median, months	30.1	27.6	43.4	39.3	46.6	46.5	38.0	34.1
Hazard ratio, 95% CI	0.96 (0.79-1.17)		0.87 (0.66-1.17)		0.90 (0.61-1.32)		0.88 (0.57-1.36)	

Presented at ESGO 2025 Annual Meeting; Feb 20-23; Milan, Italy.; Ann Oncol. 2024 Nov;35(11):981-992.

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

- Efecto sinérgico con iPARP
- No toda mutación en HRD responde a iPARP
- KELIM desfavorable y alto riesgo
- PFS2 significativo para PAOLA-1 en HRD+

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut
- KELIM favorable

¿IMPACTO DE OTROS ENDPOINT SECUNDARIOS? PFS2. ATHENA-MONO y PRIMA... Y SOLO-1

ESGO 2025

PSA-063 ATHENA-MONO Post-Progression Survival Data Update in Patients With Newly Diagnosed Advanced Ovarian Cancer

Sharad Ghamande, Rowan E. Miller, Ekaterina Solovyeva, Emily Prendergast, Maria Del Mar Gordon Santiago, Yong-Man Kim, Ramey Littell, Nuria Ruiz, Paul Bessette

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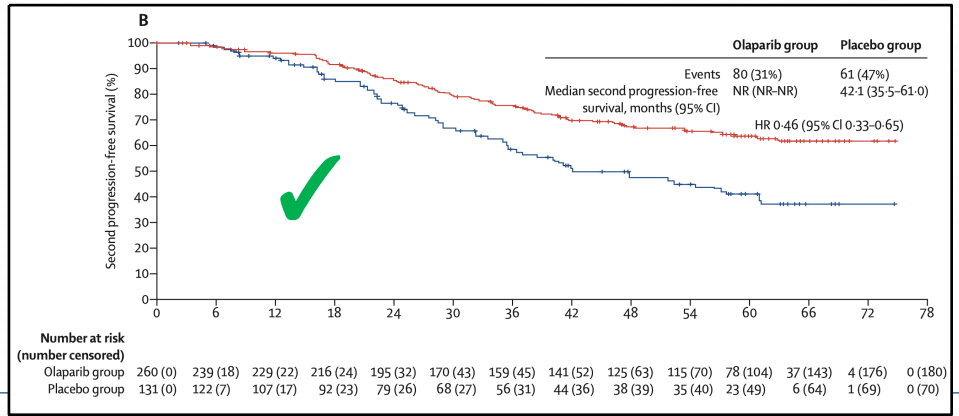
PFS2								
Median, months	30.1	27.6	43.4	39.3	46.6	46.5	38.0	34.1
Hazard ratio, 95% CI	0.96 (0.79-1.17)		0.87 (0.66-1.17)		0.90 (0.61-1.32)		0.88 (0.57-1.36)	

SOLO-1



Slides presented at: Society of Gynecologic Oncology 2021 Virtual Annual Meeting on Women's Cancer; March 19-25, 2021; virtual.

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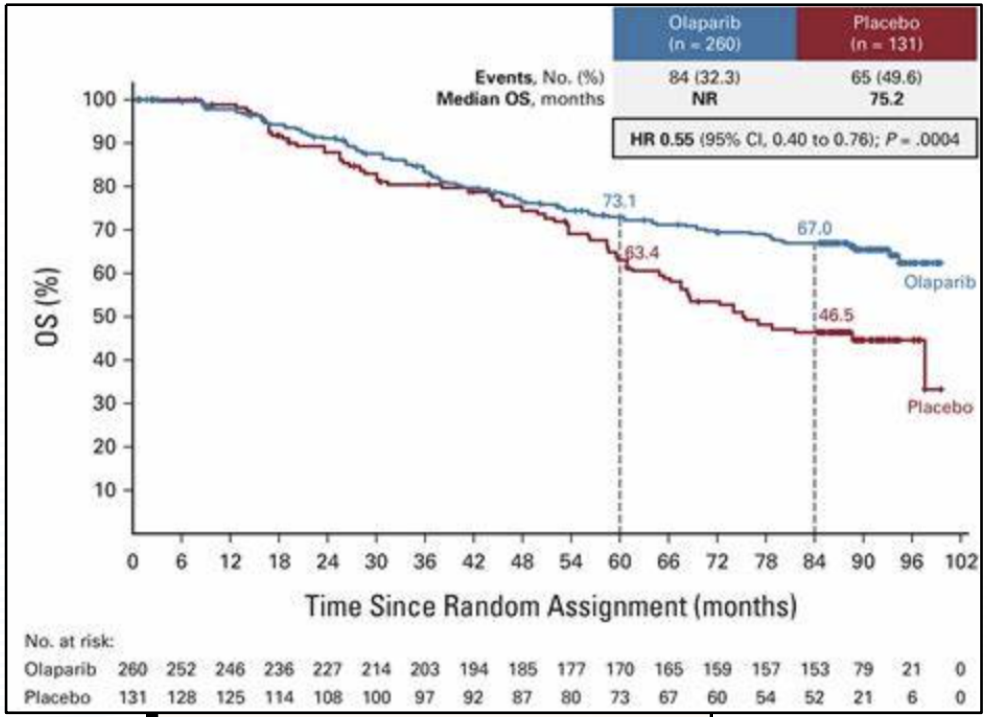
- PFS2 significativo para PAOLA-1 en HRD+

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut
- KELIM favorable
- PFS2 significativo para SOLO-1 (BRCAmut)

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV



Argumentos en contra de BV

No beneficio en QT neoadyuvante

Dudas beneficio en HRD/BRCAmut

KELIM favorable

PFS2 significativo para SOLO-1 (BRCAmut)

OS clínicamente significativo para SOLO-1

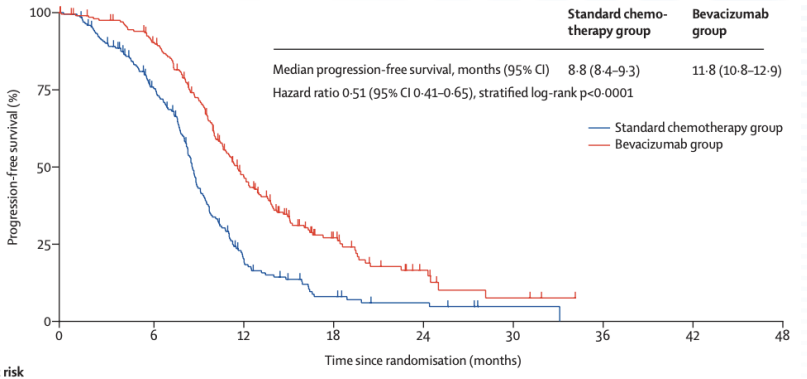
¿Y POR QUÉ NO PONER LA COMBINACIÓN? RECHALLENGE

Argumentos a favor de BV

- Efecto sinérgico con iPARP
- No toda mutación en HRD responde a iPARP
- KELIM desfavorable y alto riesgo
- PFS2 significativo para PAOLA-1 en HRD+
- Rechallenge BV: MITO16

Carboplatin-based doublet plus bevacizumab beyond progression versus carboplatin-based doublet alone in patients with platinum-sensitive ovarian cancer: a randomised, phase 3 trial

*Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Vanda Salutari, Frédèric Selle, Simona Frezzini, Ugo De Giorgi, Patricia Pautier, Alessandra Bologna, Michele Orditura, Coraline Dubot, Angiolo Gadducci, Serafina Mammoliti, Isabelle Ray-Coquard, Elena Zafarana, Enrico Breda, Laure Favier, Antonio Ardizzoia, Saverio Cinieri, Rémy Largillier, Daniela Sambataro, Emmanuel Guardiola, Rossella Lauria, Carmela Pisano, Francesco Raspagliesi, Giovanni Scambia, Gennaro Daniele, Francesco Perrone, on behalf of the MITO16b/MANGO–OV2/ENGOT–ov17 Investigators**



Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: The randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17.. JCO 36, 5506-5506(2018).

¿Y POR QUÉ NO PONER LA COMBINACIÓN? MAYOR BENEFICIO DE BV EN PROC

OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer

Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut
- KELIM favorable
- PFS2 significativo para SOLO-1 (BRCAmut)
- OS clínicamente significativo para SOLO-1
- OCEANS y AURELIA son EC positivos

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

Efecto sinérgico con iPARP

HRD+/BRCAwt
ALTO RIESGO (E. IV, ¿NACT?)
MENOR SENSIBILIDAD A PLATINO (Kelim desfavorable / Respuesta parcial tras platino)

Argumentos en contra de BV

No beneficio en QT neoadyuvante

BRCAmut
IO RIESGO
SENSIBLE (Kelim
puesta completa tras
platino)

CIA son EC positivos

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

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Argumentos en contra de BV

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3ª Jornada de Actualización EN CÁNCER GINECOLÓGICO

BUSCANDO RESPUESTAS PARA OPTIMIZAR EL TRATAMIENTO

Bilbao
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Isabelle Ray-Coquard
Centre Leon Berard
France

Bradley Monk

West Palm Beach, |
United States

Tumour Review

Optimal bevacizum[illegible] treatment strategy in advanced ovarian cancer:
A review

Bradley J. Monk [a,b,*],

[a] GOG Foundation, Philadelphia, PA, U
[b] Division of Gynecologic Oncology, Flor
[c] Gynecologic Oncology Unit, Humanitas
[d] Department of Biomedical Sciences, H
[e] Department of Gynecologic Oncology,
[f] Department of Gynecology with Center
Oncology (NOGGO) – Arbeitsgemeinsch

Conclusions and future persp

Bevacizumab is an establish
and recurrent AOC; however, id
is still debated. Recent results
bevacizumab with olaparib as m
both higher- and lower-risk pat
While the use of bevacizumab a
relevant in first-line treatment i
provided some insights into p
ment. Various factors that ma
considered (Table 4), includi
score), relevant clinical subgro
neoadjuvant vs. upfront surgery
history of cardiovascular dis
perforation or renal dysfunctio
such as NIRVANA-1 and AGO-
alize treatment with bevacizuma

Table 4
Factors that might influence use of bevacizumab.

Biomarkers	BRCAm (for use in combination with olaparib)
	HRD score (for use in combination with olaparib)
	KELIM score
Relevant clinical subgroups	Higher vs. lower risk
	Residual tumor
	Neoadjuvant vs. upfront surgery
Individual toxicity profile	Risk factors for gastrointestinal perforation
	History of cardiovascular disease, including risk factors for arterial/venous thrombosis and hypertension
	Risk factors for renal dysfunction
Contraindications for bevacizumab	History of bleeding or blood clotting disorders
	Recent surgery
	Pregnancy

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

PODCAST

Should all advanced BRCA-mutated patients in response to first-line platinum-based chemotherapy receive PARPi + bevacizumab as maintenance therapy?

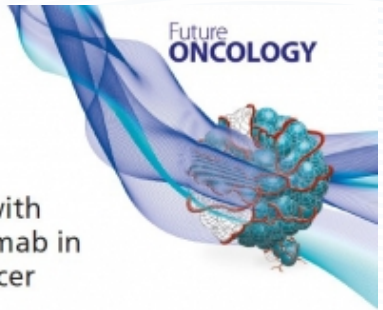
M. Turinetto[1*], I. Ray-Coquard[2] & C. Gourley[3]

[1]Department of Oncology, University of Torino at Ordine Mauriziano Hospital, Turin, Italy; [2]Centre Léon Bérard Department of Medicine and Centre de Recherche en Cancérologie de Lyon, Lyon Recherche Innovation Contre le Cancer (LYRICAN), Université Claude Bernard Lyon I, Lyon, France; [3]Nicola Murray Centre for Ovarian Cancer Research, Cancer Research UK Scotland Centre, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK

Aunque es posible argumentar que los pacientes con tumores BRCA probablemente se beneficien al máximo de PARPi y, por lo tanto, **es posible que no necesiten bevacizumab en primera línea, todavía no tenemos un prueba formal de la comparación directa,** que estará disponible con los resultados del ensayo NIRVANA-1

Candidatos a combinación:

- Estadio IV
- Respuesta parcial al platino
- Enf residual tras cirugía
- Derrame pleural



Clinical Trial Protocol

For reprint orders, please contact: reprints@futuremedicine.com

NIRVANA-1: maintenance therapy with niraparib versus niraparib-bevacizumab in patients with advanced ovarian cancer

Syrine Sghaier[1,2], Pauline Corbaux[1,2], Isabelle Ray-Coquard[3], Myong Cheol Lim[4], Kosei Hasegawa[5], Els Van Nieuwenhuysen[6], Antonio Gonzalez[7], Francesco Raspagliesi[8] & Gilles Freyer*[1,2]

https://doi.org/10.1016/j.esmoop.2024.102983

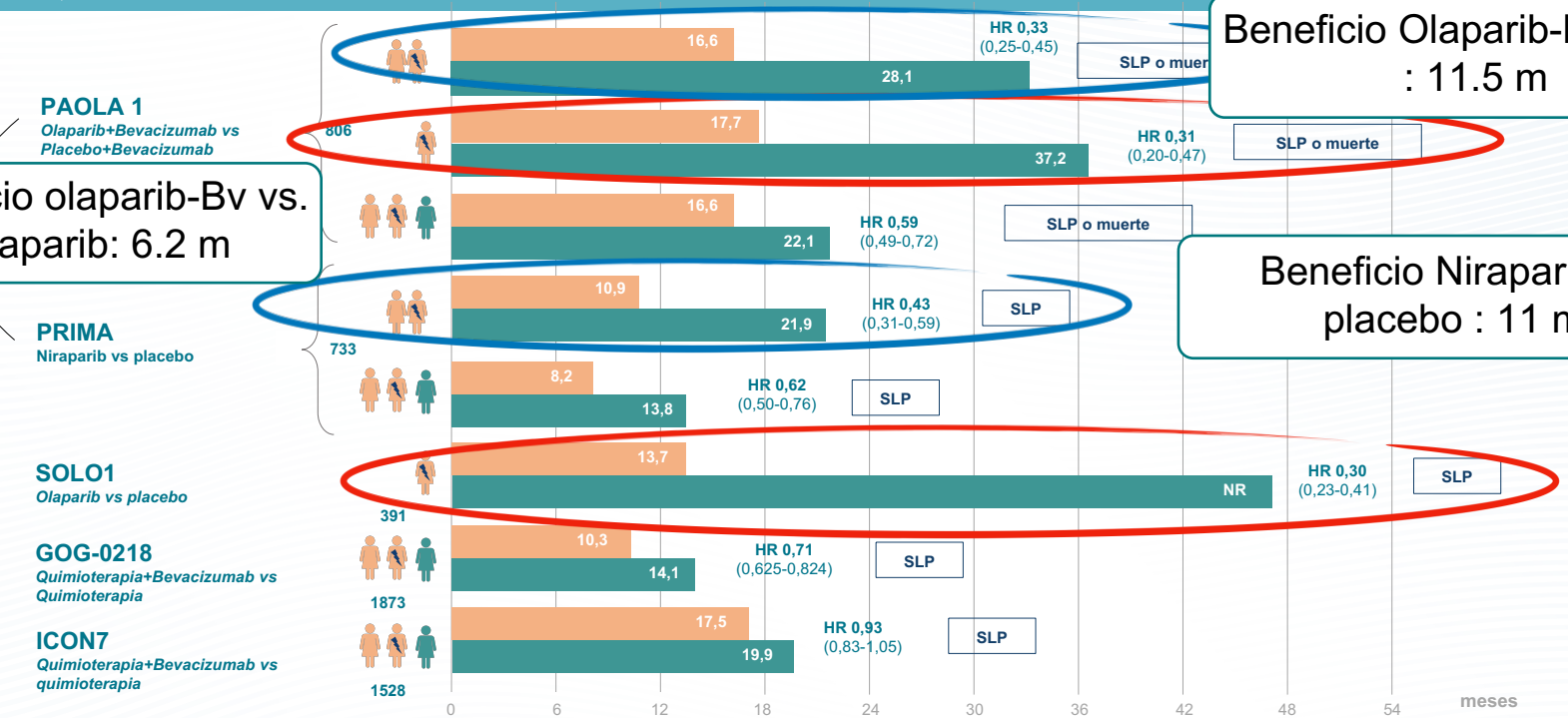
Mujer sin comorbilidades. Ca seroso de ovario alto grado E. IIIC, NACT, HRD +, CRS2. ¿Le pongo Bv?

COMPARACIONES INDIRECTAS DE PFS

Beneficio olaparib-Bv vs. Niraparib: 6.2 m

Beneficio Olaparib-Bv vs. Bv : 11.5 m

Beneficio Niraparib vs placebo : 11 m



Adaptado de Nero C, *et al.* Cancers (Basel). 2021[1]

Referencia: **1.** Nero C, Ciccarone F, Pietragalla A, *et al.* Ovarian Cancer Treatments Strategy: Focus on PARP Inhibitors and Immune Check Point Inhibitors. Cancers (Basel). 2021 Mar 15;13(6):1298.

La SUPERVIVENCIA (PFS/OS) viene determinada por:

- El fármaco a estudio
- **LAS CARACTERÍSTICAS INTRÍNSECAS DE LA POBLACIÓN**

	SOLO-1	PAOLA-1	ATHENA-MONO	PRIMA
E. IV (%)	17	30	25	35
PDS	63	51	49	33
R2 (%)	23	40	25	47
NAC (%)	35	42	51	67
Respuesta parcial	18	27	18	31
BRCAwt	0	70	79	70

BAJO RIESGO

> OS

Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ ENGOT-ov25 trial

ALTO RIESGO

< OS

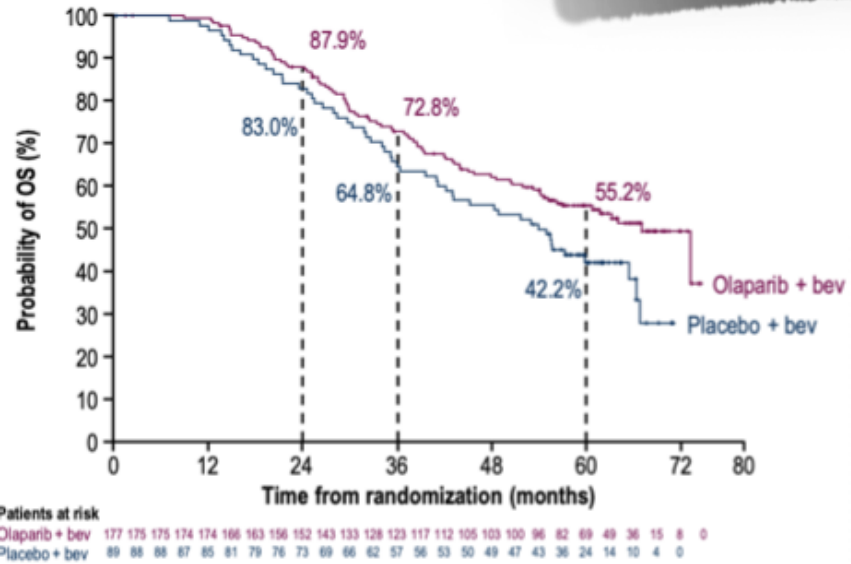
COMPARACIONES INDIRECTAS ENTRE ESTUDIOS: OS HRD+ EN PAOLA-1 (alto riesgo) vs. PRIMA

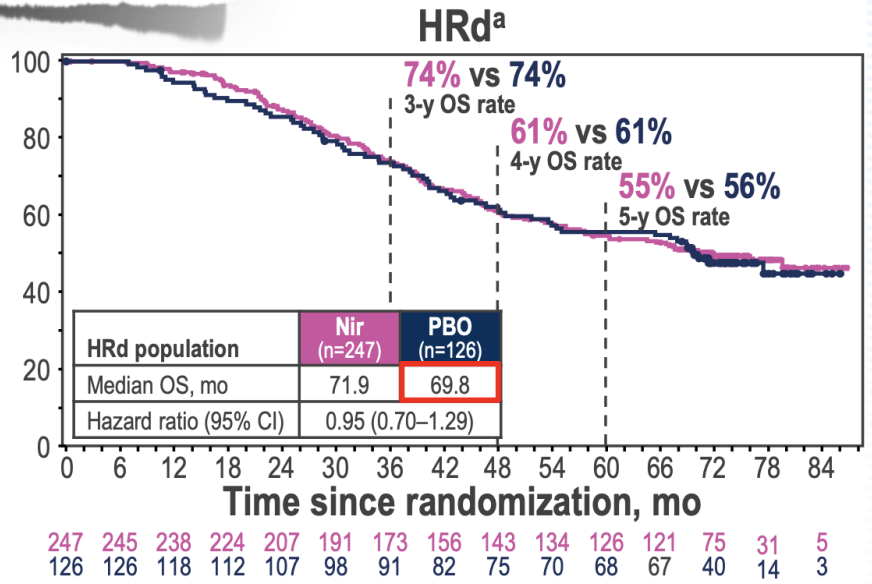
PAOLA-1 HRD+ ALTO RIESGO

OS a 5 años:

- PAOLA-1, brazo Olaparib-BV: **55.2%**
- PRIMA, brazo Niraparib: **55%**

PRIMA HRD+





D'Orusso. Esmo-Gyn. 2022
González-Martín A, et al. presented at ESMO 2024 13 -17 September, Barcelona

COMPARACIONES INDIRECTAS ENTRE ESTUDIOS: PFS en OVARIO vs PRIMA

Design: Phase II, Single-Arm, Open-Label Study

Patients with newly diagnosed high-grade serous or endometrioid stage IIIB or IV epithelial ovarian, fallopian tube, or peritoneal cancer who achieved a CR, PR, or NED result after front-line platinum-based chemotherapy + bevacizumab (N=105)

All patients underwent tissue testing for HRD status at enrollment

Niraparib (200 or 300 mg QD) + bevacizumab (15 mg/kg Q3W)

Niraparib starting dose

200 mg: <77 kg and/or platelet count <150,000/μL

300 mg: All others

Bevacizumab

Maximum of 15 months, including first-line treatment

Endpoint		Data cutoff
Efficacy	PFS rate at 18 months[a]	December 24, 2020
	Median PFS	June 16, 2021
Safety	Treatment-related AEs	December 24, 2020

[a]Primary endpoint.

ASCO 2025. Póster

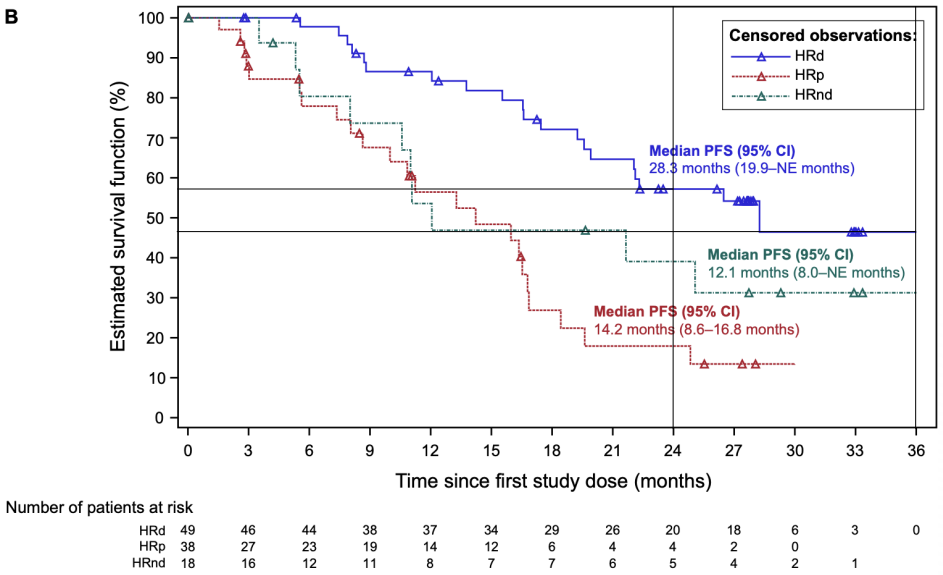
OVARIO
Estadio IV 21,9%
PDS 37,1%
R2 26,7%
PR 41,9%
BRCAwt 63,8%

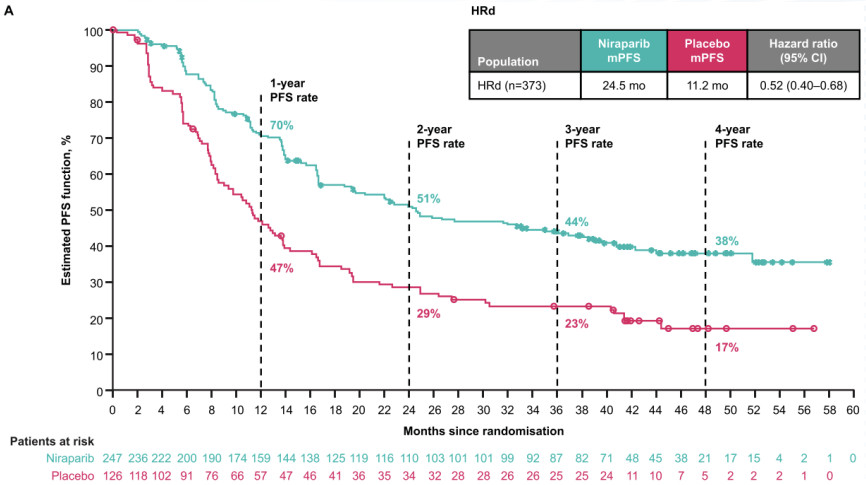
PRIMA
Estadio IV 35%
PDS 33%
R2 47%
PR 31%
BRCAwt 70%

COMPARACIONES INDIRECTAS ENTRE ESTUDIOS: PFS en OVARIO vs PRIMA

mPFS

- OVARIO, brazo Niraparib-BV: **28.3 m**
- PRIMA, brazo Niraparib: **24.5 m**





Mujer sin comorbilidades. Ca seroso de ovario alto grado E. IIIC, NACT, HRD +, CRS2. ¿Le pongo Bv?

CUANDO NO SEPAS QUÉ HACER…

OVARIO TRIAL VS. PRIMA EN HRD+ (SEGÚN GPT 4.0)

📌 **OVARIO (niraparib + bevacizumab) – HRD**

- N = 49
- Mediana PFS = 28.3 meses
- Eventos (progresión o muerte) ≈ 49% → Aproximadamente 24 eventos (ya que la madurez era del 50.5%)
- Diseño: fase II, no controlado

📌 **PRIMA (niraparib) – HRD**

- N = 245 (niraparib en HRD)
- Mediana PFS = 21.9 meses
- Eventos (progresión o muerte) = 154 (según texto: "primary analysis was performed after progression or death in 154 patients with HRD")
- Diseño: fase III, controlado

📊 Análisis estadístico aproximado – comparación de tasas de eventos

Queremos comparar las proporciones de eventos en ambos grupos:

- OVARIO: 24/49 ≈ **49%**
- PRIMA: 154/245 ≈ **62.9%**

Podemos aplicar una prueba de diferencia de proporciones (prueba z para dos proporciones).

🧮 Cálculo

Usamos:

$$z = \frac{p_1 - p_2}{\sqrt{p(1-p)(\frac{1}{n_1} + \frac{1}{n_2})}}$$

donde:

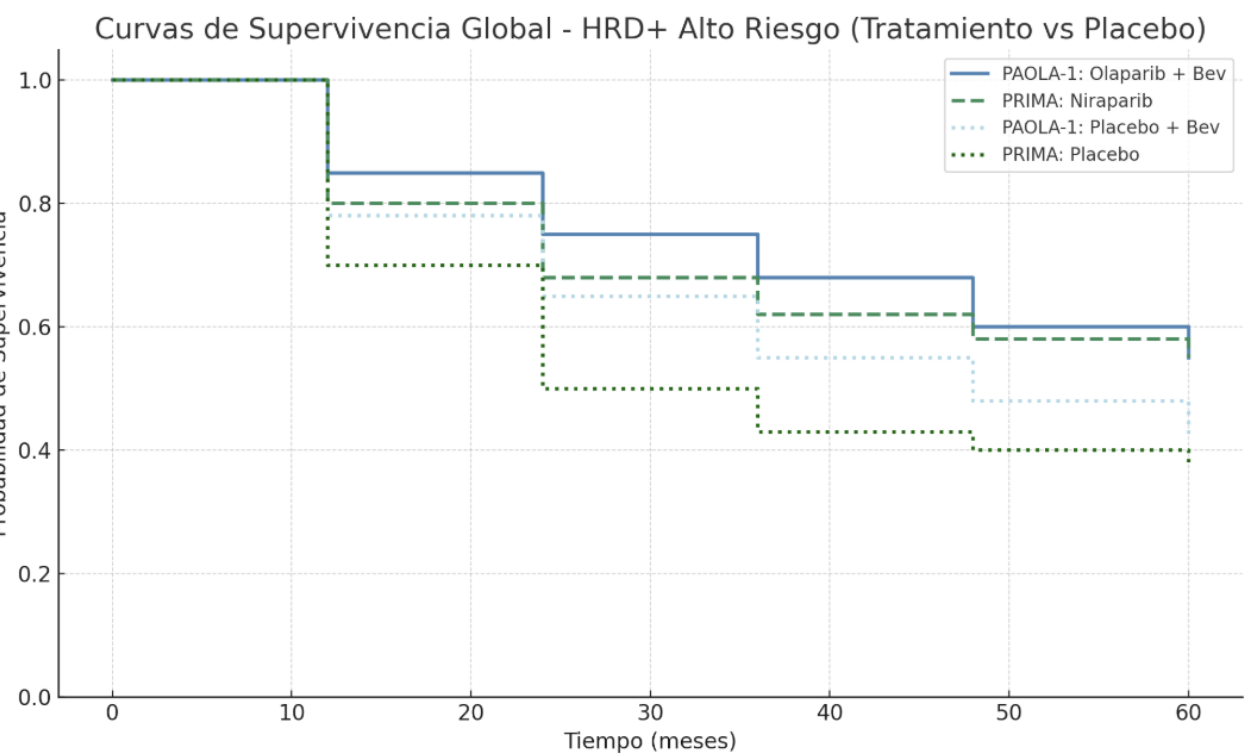
- $p_1 = 0.49, n_1 = 49$
- $p_2 = 0.629, n_2 = 245$
- $p = \frac{24+154}{49+245} = \frac{178}{294} \approx 0.605$

Sustituimos:

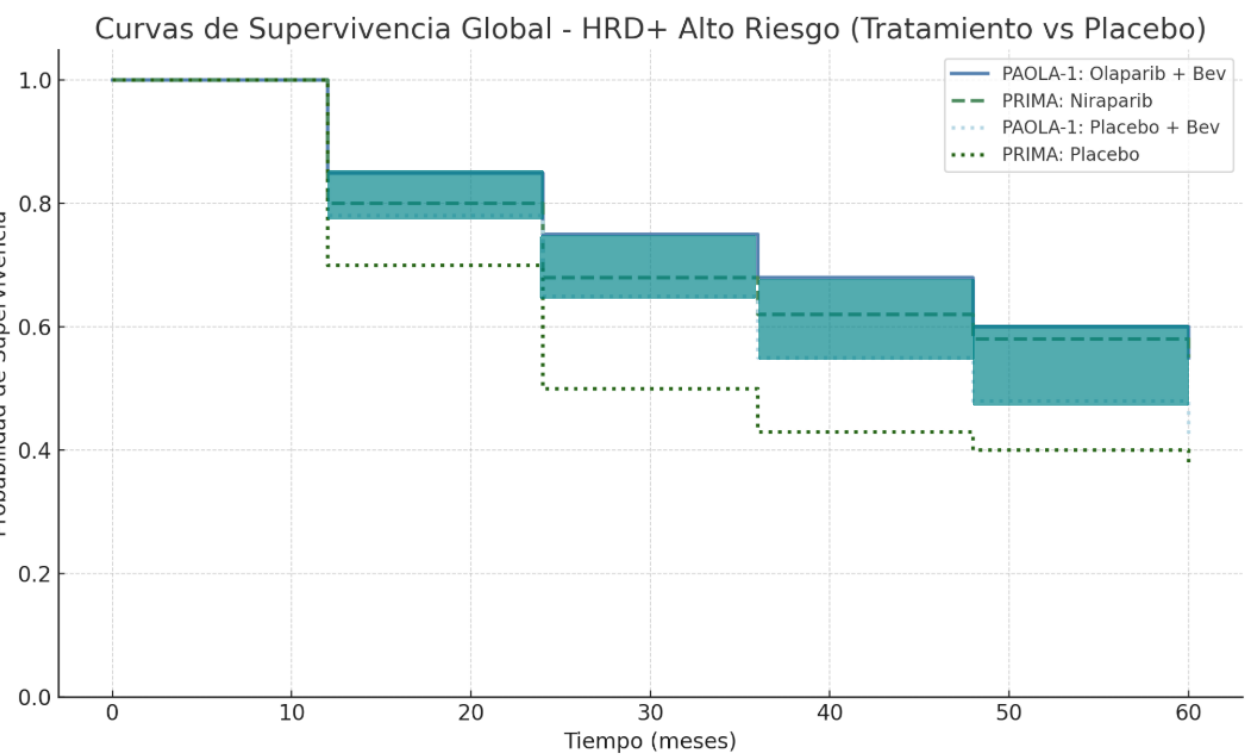
$$z = \frac{0.49 - 0.629}{\sqrt{0.605(1-0.605)(\frac{1}{49} + \frac{1}{245})}} \approx \frac{-0.139}{\sqrt{0.239(0.0245 + 0.0041)}} \approx \frac{-0.139}{\sqrt{0.00676}} \approx \frac{-0.139}{0.0822} \approx -1.69$$

Esto da un valor de **p ≈ 0.09**, lo que **no alcanza significación estadística al 5%**, aunque es cercano.

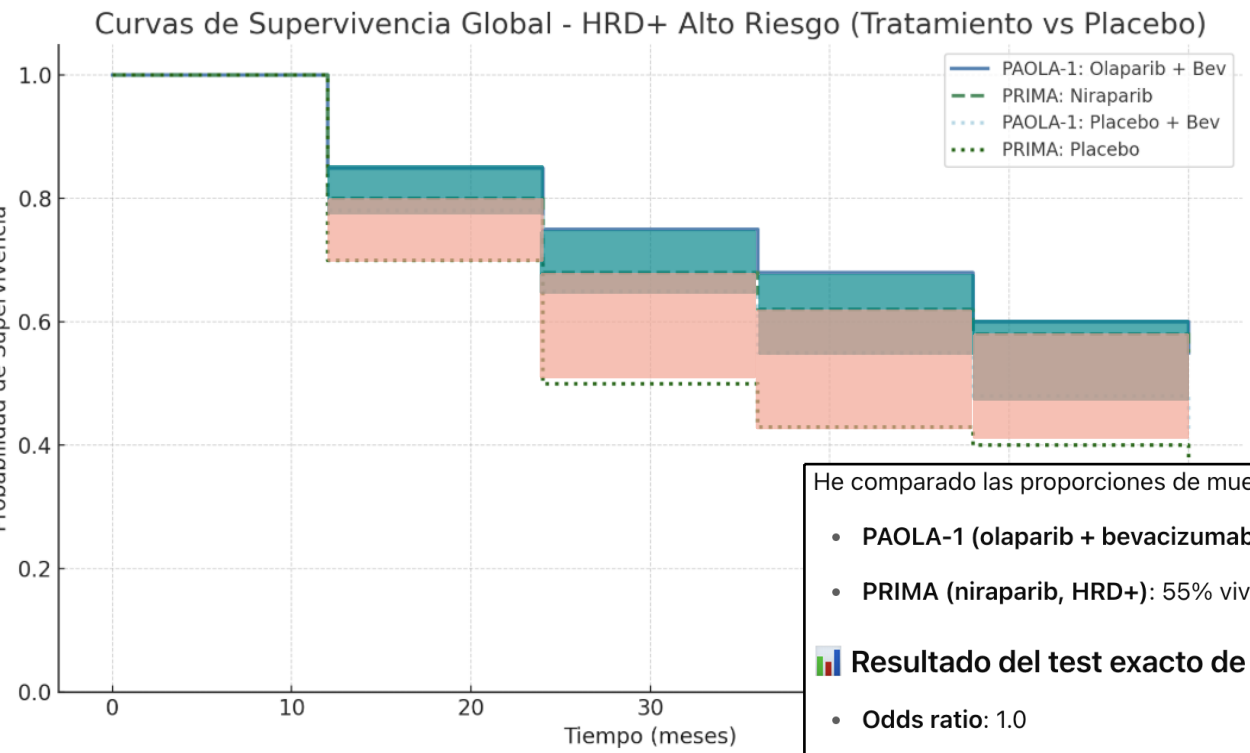
OS PAOLA-1 ALTO RIESGO HRD+ vs. PRIMA HRD+ (SEGÚN GPT 4.0)



OS PAOLA-1 ALTO RIESGO HRD+ vs. PRIMA HRD+ (SEGÚN GPT 4.0)



OS PAOLA-1 ALTO RIESGO HRD+ vs. PRIMA HRD+ (SEGÚN GPT 4.0)



He comparado las proporciones de muertes a los 5 años entre los dos brazos que mencionaste:

- **PAOLA-1 (olaparib + bevacizumab, HRD+ alto riesgo)**: 55% vivas → 45% muertas
- **PRIMA (niraparib, HRD+)**: 55% vivas → 45% muertas

📊 Resultado del test exacto de Fisher:

- **Odds ratio**: 1.0
- **Valor p**: 1.0

¿APORTA ALGO EL BEVACIZUMAB EN HRD+?

Argumentos a favor de BV

- Efecto sinérgico con iPARP
- No toda mutación en HRD responde a iPARP
- KELIM desfavorable y alto riesgo
- PFS2 significativo para PAOLA-1 en HRD+
- Rechallenge BV: MITO16

Argumentos en contra de BV

- No beneficio en QT neoadyuvante
- Dudas beneficio en HRD/BRCAmut
- KELIM favorable
- PFS2 significativo para SOLO-1 (BRCAmut)
- OS clínicamente significativo para SOLO-1
- OCEANS y AURELIA son EC positivos
- CHAT GPT dice que BV no aporta

CONCLUSIONES

- **iPARP en monoterapia o en combinación con bevacizumab son opciones válidas** como tratamiento de mantenimiento en pacientes HRD+

- Es **más discutible** el papel de la combinación en pacientes **BRCAmut** (resultados de PFS, PFS2 y OS de SOLO-1)

- Existen factores, como la **platino-sensibilidad (KELIM)** o el **alto riesgo** que definen mejor el subgrupo de pacientes que más se benefician de la combinación (estudios retrospectivos, post-hoc…)

CONCLUSIONES

- En los próximos años, debido al "boom" de nuevos fármacos/EC en marcha en cáncer de ovario/ estudios basket es probable que existan distintas terapias (diferente mecanismo de acción, diferente toxicidad…) con beneficio para la misma indicación.

GLORIOSA: A randomized, open-label, phase 3 study of mirvetuximab soravtansine with bevacizumab vs. bevacizumab as maintenance in platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer.

Authors: David M. O'Malley, Tashanna K. N. Myers, Claudio Zamagni, Elisabeth Diver, and Domenica Lorusso | AUTHORS INFO & AFFILIATIONS

La ciencia nos enseña, en efecto, a someter nuestra razón a la verdad y a conocer y juzgar las cosas tal como son, es decir, como ellas mismas eligen ser y no como quisiéramos que fueran.

Miguel de Unamuno.

Plaza Miguel de Unamuno.
Casco Viejo. Bilbao