AXIS Medical Education

Improving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer:

Cytogenetic Testing and PARP Inhibition for Maintenance Treatment

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Agenda

- What Is Cytogenetic Testing and Why Should I Use It? Identification of Patients Who Might Benefit from PARP Inhibitor Therapy
- Where Do PARP Inhibitors Fit in the Treatment Paradigm of Ovarian Cancer? Practical Strategies
- Clinical Data for PARP Inhibitors as Maintenance Therapy for Newly-Diagnosed Advanced Ovarian Cancer
- PARP Inhibitors as Maintenance Therapy and Treatment for Relapsed/Recurrent Advanced Ovarian Cancer

Learning Objectives

- Utilize molecular profiling to guide treatment selection for first-line maintenance therapy with PARP inhibitors
- Incorporate PARP inhibitors into treatment plans for first-line maintenance therapy of advanced ovarian cancer based on updated clinical data, guideline recommendations, and patient- and disease-related features
- Integrate early consultation to gynecologic oncologists for molecular profiling, patient selection, and communication of evidence-based treatment selection for first-line maintenance treatment of advanced ovarian cancer with PARP inhibitors
- Summarize the latest evidence supporting FDA revisions and clinical practice guideline implications regarding the role of PARP inhibitors in patients with recurrent ovarian cancer

What Is Genetic Testing and Why Should I Use It?

Identification of Patients Who Might Benefit from PARP Inhibitor Therapy

Guidelines: Tumor Molecular Analyses

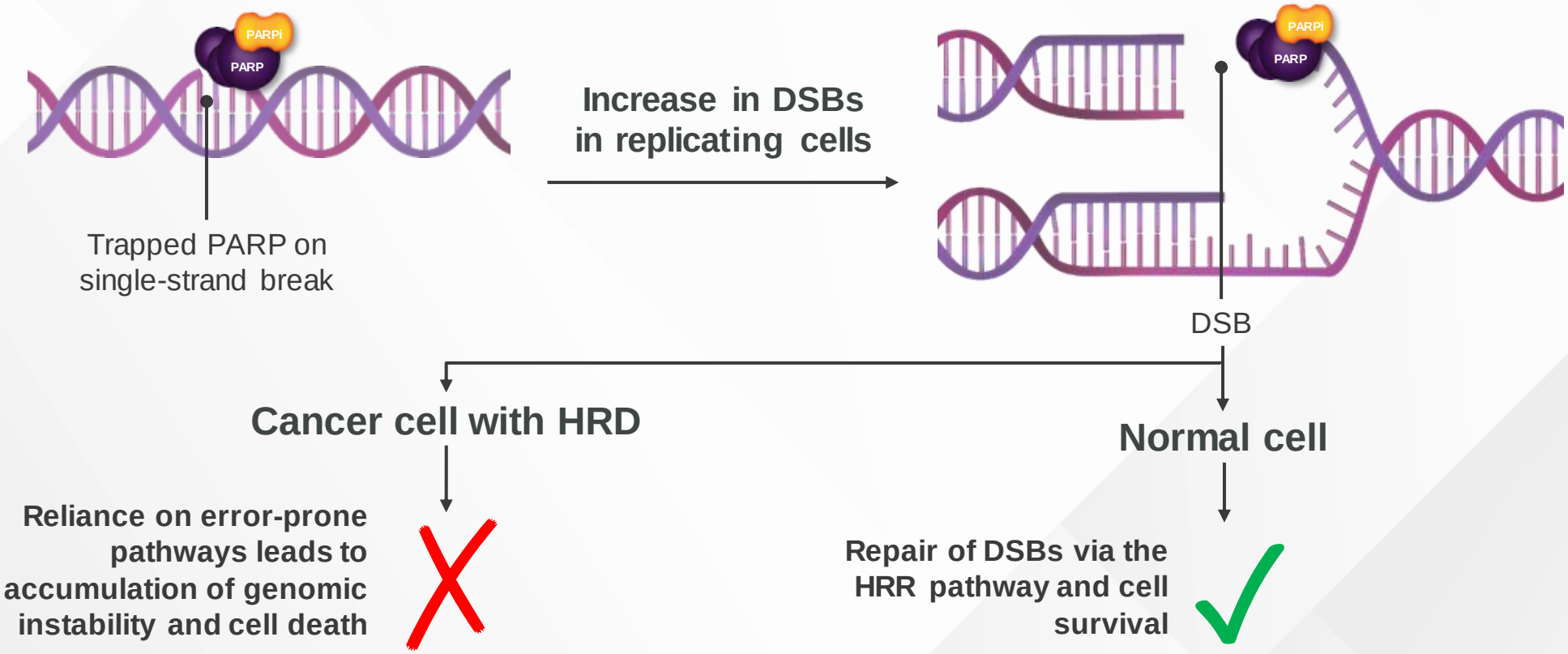
- Patients with ovarian cancer should have genetic risk evaluation and germline and somatic testing
- Germline and somatic BRCA1/2 status informs maintenance therapy
- In the absence of a BRCA1/2 mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy

Setting	Recommendation
Upfront	Choice of somatic testing should, at a minimum, optimize identification of molecular alterations that can inform use of interventions that have demonstrated benefit in this setting, including: **BRCA1/2, LOH, or HRD status in the absence of a germline BRCA mutation**
Recurrence	Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including: **BRCA1/2, HRD status, MSI, MMR, TMB, BRAF, FRα, RET, and NTRK if prior testing did not include these markers**

Armstrong DK, et al. NCCN Guidelines on Ovarian Cancer. Version 2.2023.
FRα, folate receptor alpha; HRD, homologous recombination deficiency; LOH, hoss of heterozygosity; MSI, microsatellite instability; MMR, mismatch repair; PARP, poly(ADP-ribose) polymerase; TMB, tumor mutational burden.

PARP Inhibition Selectively Targets Tumors With Homologous Recombination Deficiency

PARPi trap PARP enzymes on DNA, causing cancer-specific cell death in tumors with HRD

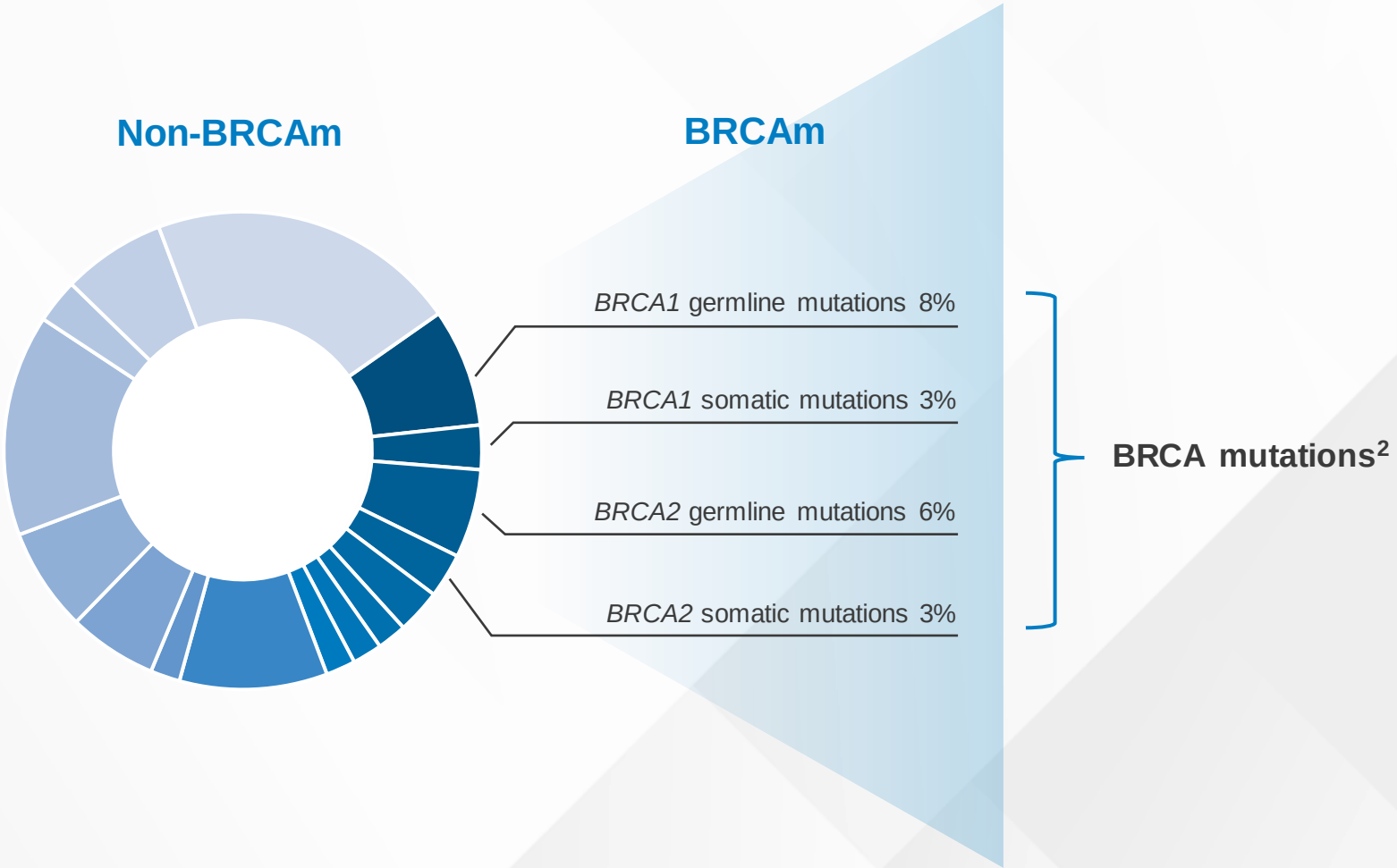


O'Connor MJ. *Mol Cell.* 2015;60(4):547-560.

DSB, double-strand break; HRD, homologous recombination deficiency; HRR, homologous recombination repair; PARPi, poly(ADP-ribose) polymerase inhibitor.

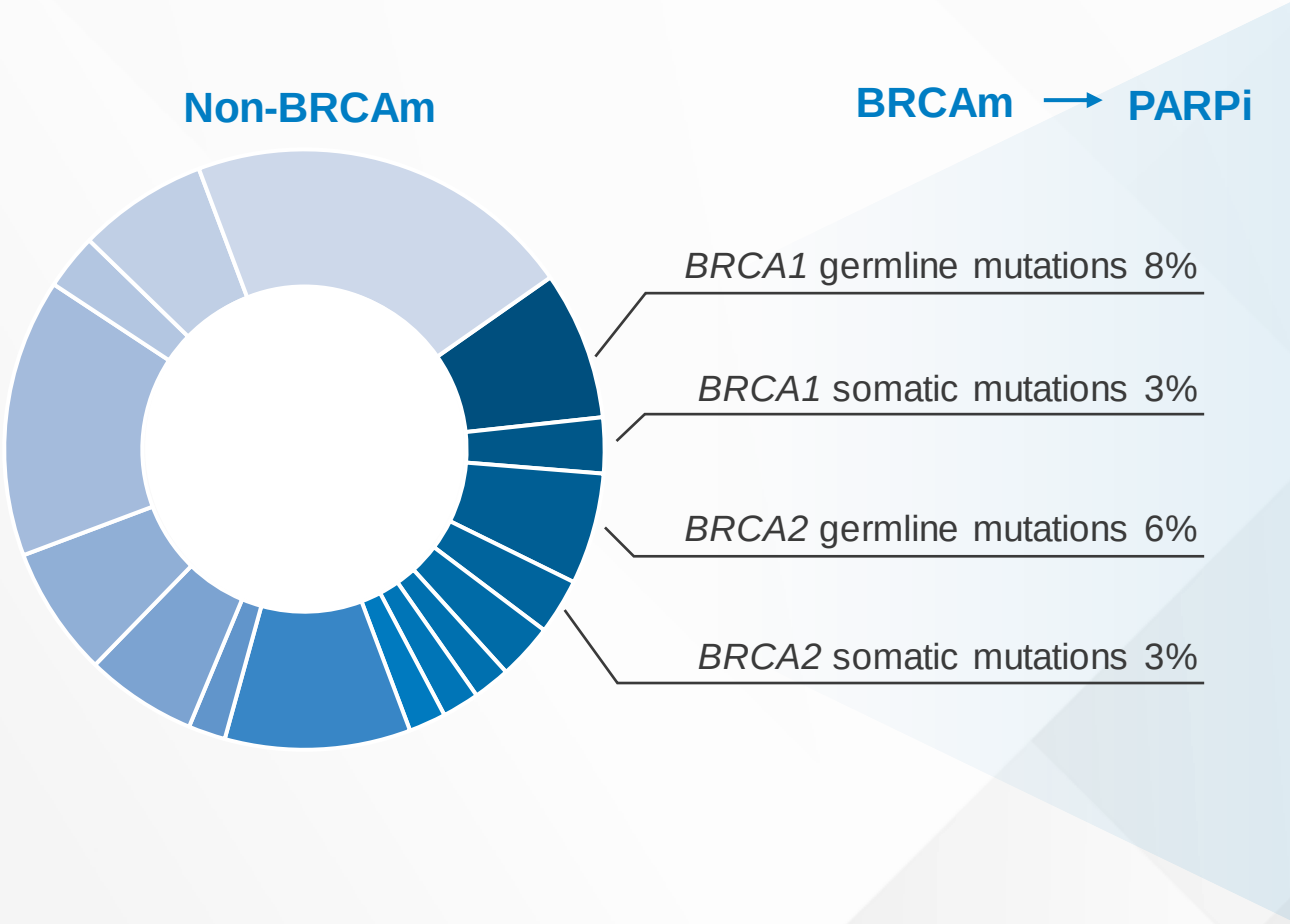
Who Should Be Treated With PARPi?

Approximately 20% of Patients With Ovarian Cancer Harbor a BRCAm[1,2]



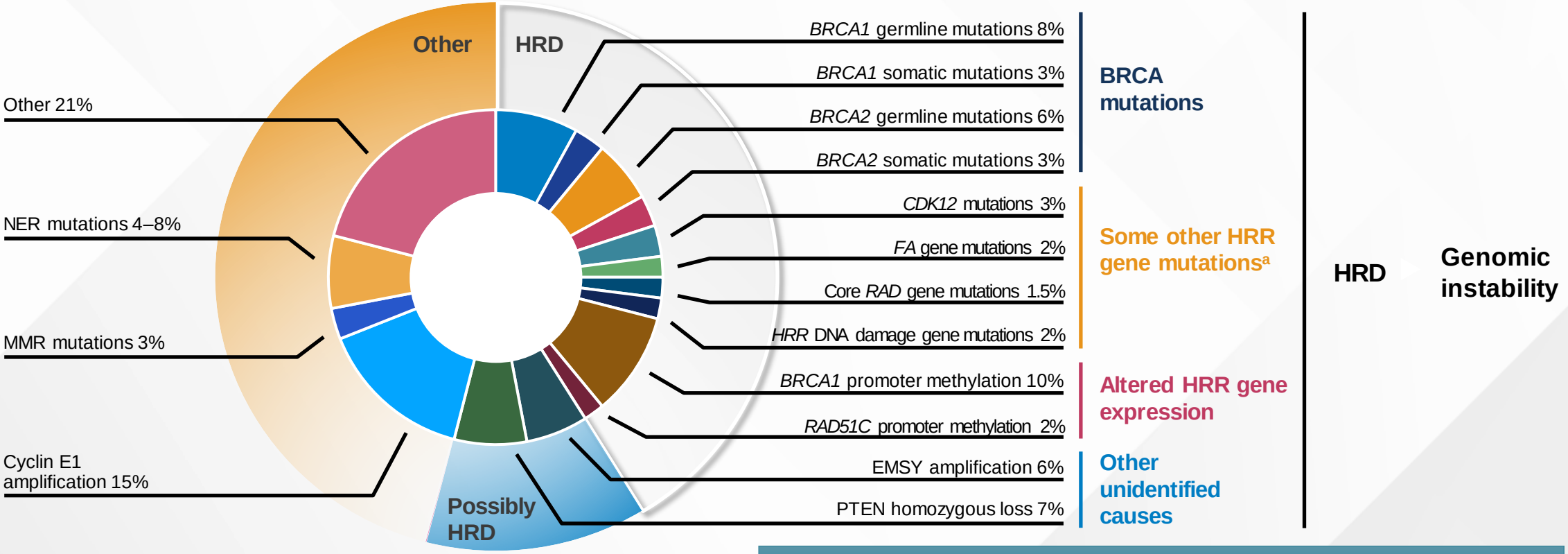
1. Miller RE, et al. *Ann Oncol.* 2020;31(12):1606-1622. 2. Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5:1137-1154.
BRCA(m), BRCA1 and/or BRCA2 (mutation); PARPi, poly(ADP-ribose) polymerase inhibitor.

But What About the ~80% Without a BRCA Mutation?



Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5(11):1137-1154.
BRCA(m), *BRCA1* and/or *BRCA2* (mutation); PARPi, poly(ADP-ribose) polymerase inhibitor.

HRR Gene Mutations, Altered Gene Expression and Other Causes Contribute to Genomic Instability[1]



Actionable mutations are at a low frequency in HGSOC; therefore, genomic instability remains a key therapeutic target[2]

[a]Not all mutations have been linked to an HRD phenotype.

Image adapted from Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5(11):1137-1154.

1. Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5(11):1137-1154. 2. Press JZ, et al. *BMC Cancer.* 2008;8:17.

BRCA, *BRCA1* and/or *BRCA2*; DNA, deoxyribonucleic acid; BRCA2-interacting transcriptional repressor; FA, Fanconi anemia; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; HRR, homologous recombination repair; MMR, mismatch repair; NER, nucleotide excision repair; PTEN, phosphatase and tensin homolog.

Testing for HRD: HRR Gene Panels Are ‘Cause’ Assays, Whereas HRD Genomic Instability Tests Are ‘Effect’ Assays

HRR gene panel test

Look for the **cause** of HRR loss[1]

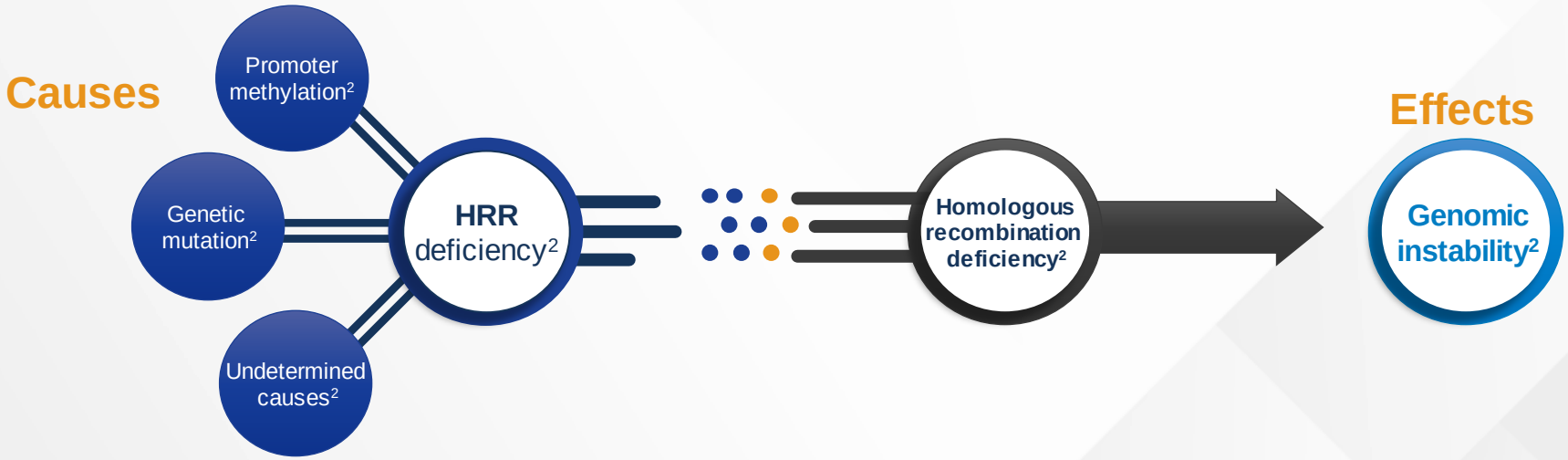
Identify pathogenic mutations in HRR genes[1]

HRD genomic instability

Look for the **effect** of HRR loss[1]

Quantify genomic aberrations that are characteristic of HRD,[1] sometimes referred to as a genomic scar test[1]

Should be done in combination with BRCA testing[3]

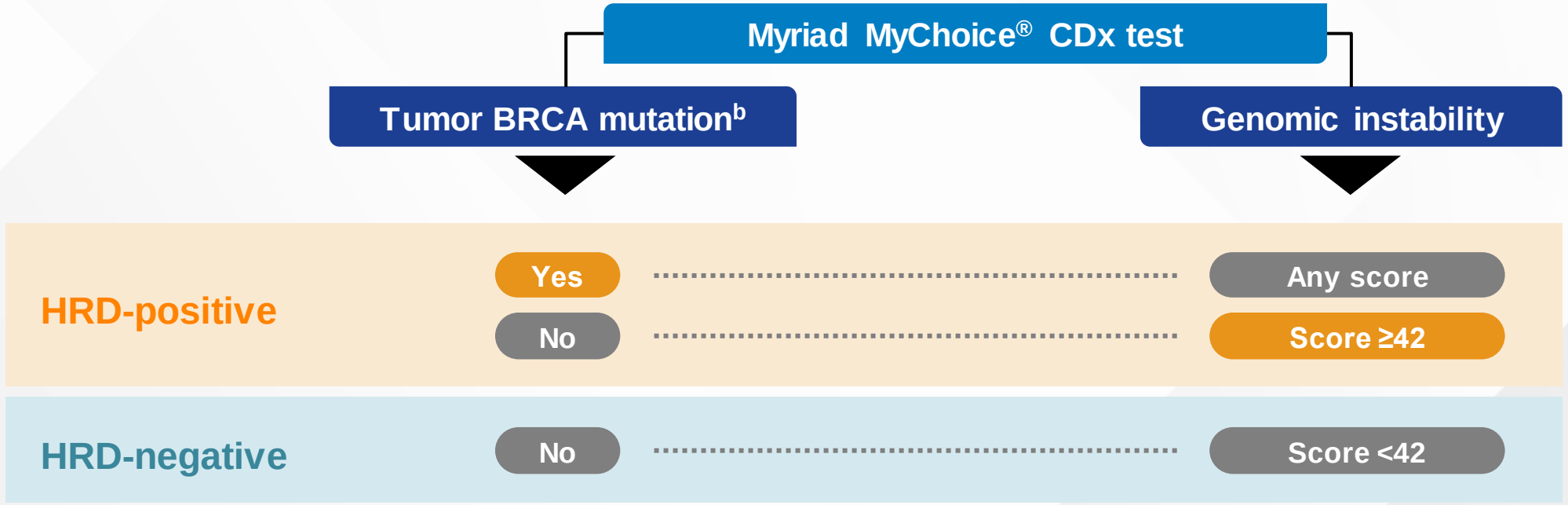


1. Pellegrino B, et al. *ESMO Open.* 2019;4(2):e000480. 2. Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5(11):1137-1154. 3. Myriad myChoice® HRD Technical Specifications. Accessed March 2022. https://myriad-web.s3.amazonaws.com/myChoice/downloads/myChoiceHRDTechSpecs.pdf

BRCA, BRCA1 and/or BRCA2; HRD, homologous recombination deficiency; HRR, homologous recombination repair.

The PAOLA-1 and PRIMA Trials in Ovarian Cancer Both Incorporated the Myriad MyChoice® CDx Test to Define the HRD Status of Patients[1-3]

The Myriad MyChoice® CDx test defines patients as HRD-positive if they have a BRCAm and/or a genomic instability score ≥42[1,a]



[a]The European Medicines Agency has authorised olaparib in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab, and whose cancer is associated with HRD-positive status defined by either a BRCAm and/or genomic instability. HRD-positive status can be defined by a composite GIS for HRD-associated genomic alterations tested by an experienced laboratory using a validated test.[4]

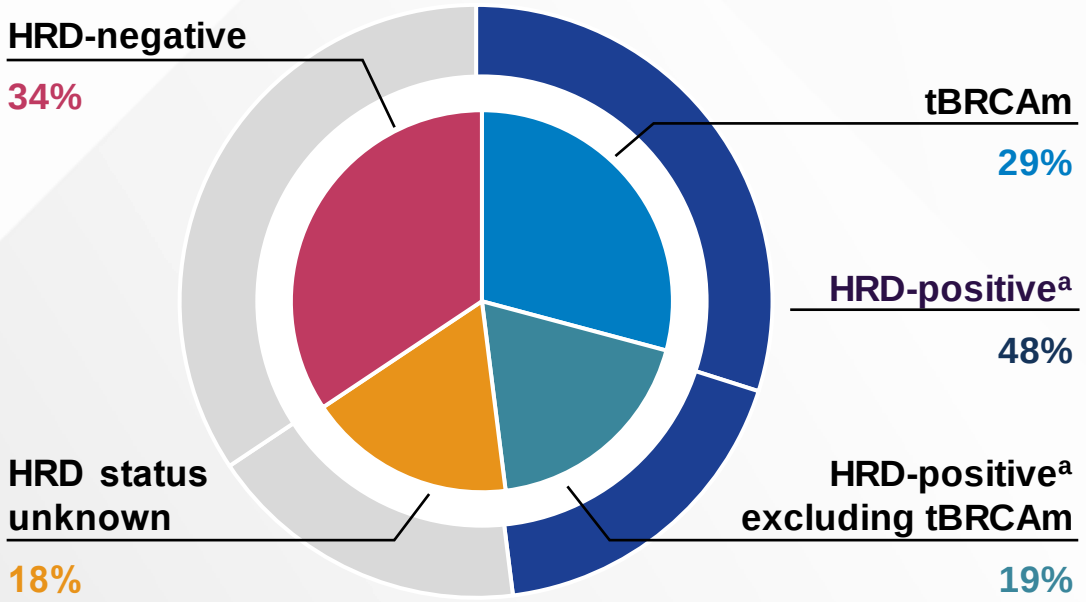
[b]As well as BRCA, the Myriad myChoice® Plus CDx analyses additional genes associated with the DNA damage response and microsatellite instability.[5] However, these do not contribute to the HRD status.

1. Ray-Coquard I, et al. ESMO Congress 2019. Abstract LBA2_PR. 2. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 3. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-2164. 4. AstraZeneca UK Limited. Lynparza (olaparib) Summary of Product Characteristics 2021. 5. Myriad Genetics Announces Expanded Research Collaboration with AstraZeneca. http://www.globenewswire.com/news-release/2018/01/03/1281459/0/en/Myriad-Genetics-Announces-Expanded-Research-Collaboration-with-AstraZeneca.html

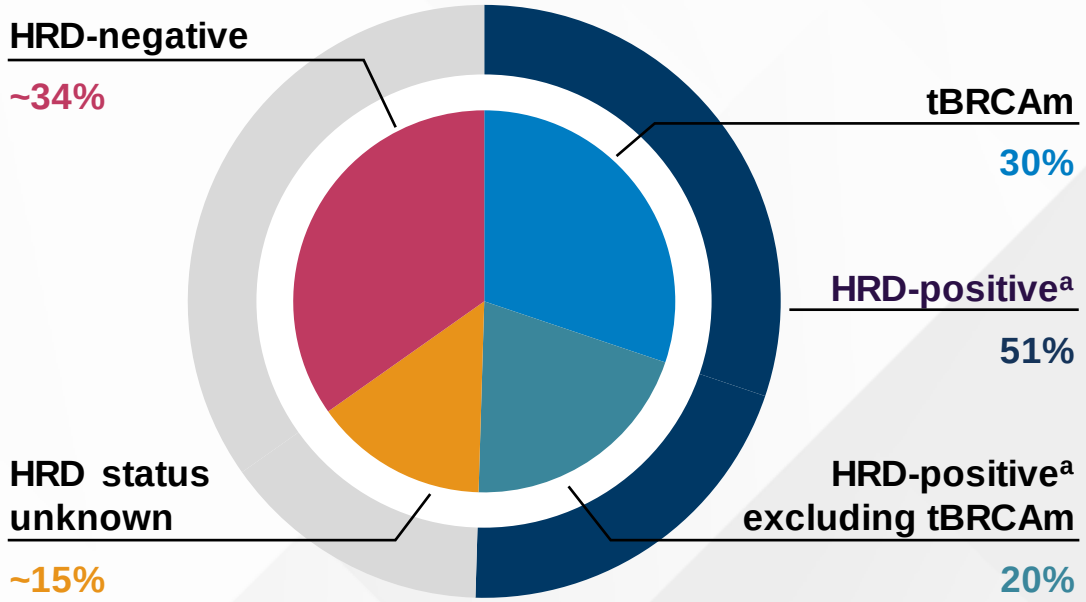
BRCA(m), *BRCA1* and/or *BRCA2* (mutation); CDx, companion diagnostic; DNA, deoxyribonucleic acid; FIGO, International Federation of Gynecology and Obstetrics; GIS, genomic instability score; HRD, homologous recombination deficiency.

Homologous Recombination Deficiency is Present in ~50% of Newly-Diagnosed, High-Grade, Epithelial Ovarian Cancers

PAOLA-1[1]



PRIMA[2]

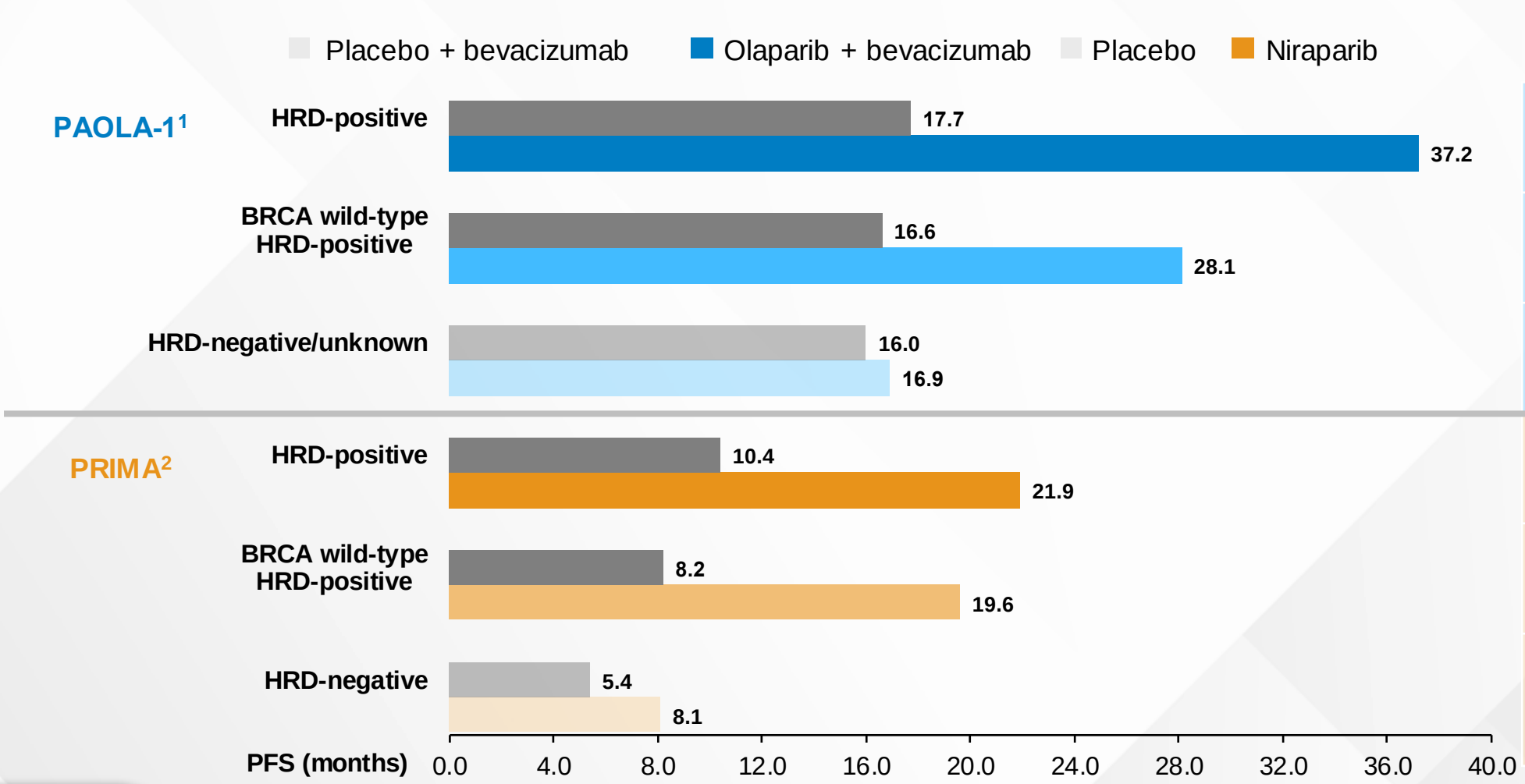


[a]HRD-positive determined by tBRCAm and/or genomic instability score ≥42 in the Myriad myChoice® companion diagnostic test.

1. Ray-Coquard I, et al. ESMO Congress 2019. Abstract LBA2_PR. 2. González-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-2402.

HRD, homologous recombination deficiency; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

In the First-Line Maintenance Setting, HRD Genomic Instability Clearly Predicts the Magnitude of PARPi Benefit



	mPFS Δ (mo)	PFS HR
PAOLA-1[1] HRD-positive	19.5	0.33
PAOLA-1[1] BRCA wild-type HRD-positive	11.5	0.43
PAOLA-1[1] HRD-negative/unknown	0.9	0.92
PRIMA[2] HRD-positive	11.5	0.43
PRIMA[2] BRCA wild-type HRD-positive	11.4	0.50
PRIMA[2] HRD-negative	2.7	0.68[a] (HR in HRD status unknown 0.85)[3]

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. [a]PRIMA was stratified by HRD status positive or negative/unknown.

1. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. 2. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 3. González-Martín A, et al. ESMO Congress 2019. Abstract #4627.

HR, hazard ratio; HRD, homologous recombination deficiency; mPFS, median progression-free survival; PARPi, poly(ADP-ribose) polymerase inhibitor.

Where Do PARP Inhibitors Fit in the Treatment Paradigm of Ovarian Cancer?

Practical Strategies

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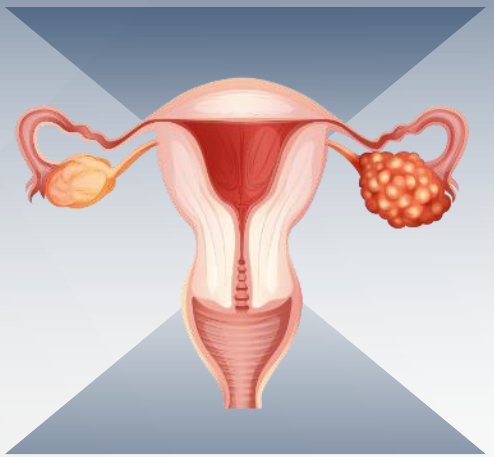
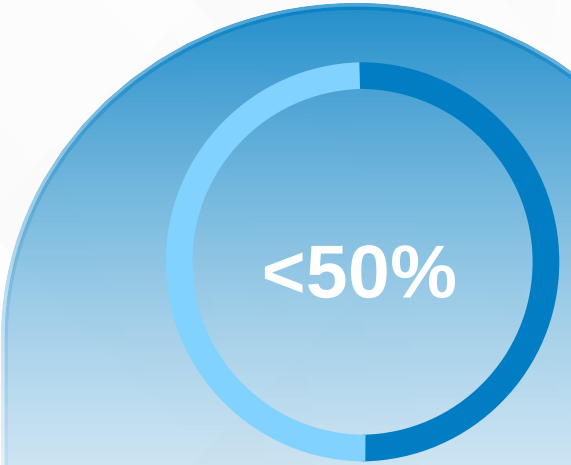
Most Patients With Advanced Ovarian Cancer Relapse Following First-Line Multimodality Therapy

Over **300,000** women were **diagnosed** with ovarian cancer in 2020[1]



At least **60%** of newly diagnosed women will have **advanced disease**[2]

~70% **of women relapse** within 3 years of first-line treatment[3]



5-year survival for newly diagnosed advanced ovarian cancer[2,4]

There is a significant need for better first-line treatment to improve outcomes for women with ovarian cancer[2,3,5-8]

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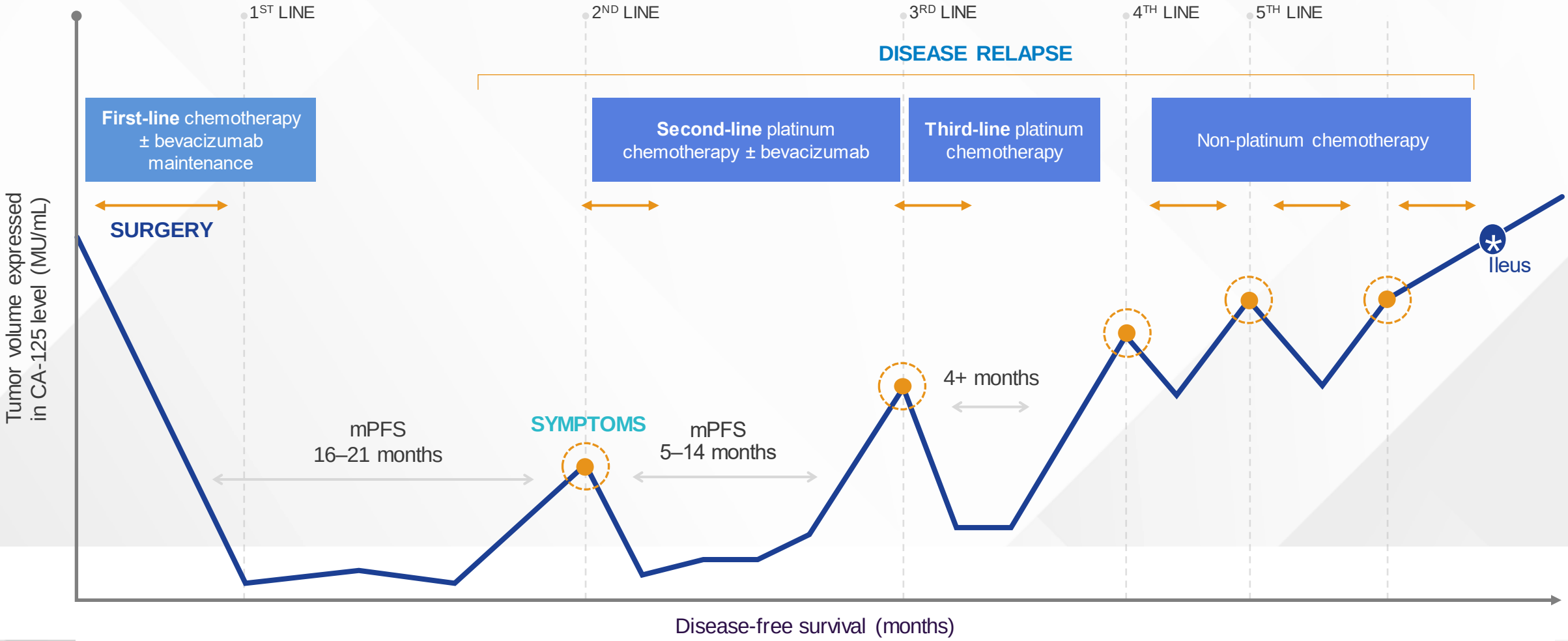
1. Sung H, et al. *CA Cancer J Clin.* 2021;71(3):209-249. 2. du Bois A, et al. *Cancer.* 2009;115(6):1234-1244. 3. Ledermann JA, et al. *Ann Oncol.* 2013;24(Suppl 6):vi24-vi32. 4. Torre LA, et al. *CA Cancer J Clin.* 2018;68(4):284-296. 5. Tewari KS, et al. *J Clin Oncol.* 2019;37(26):2317-2328. 6. Bookman MA, et al. *J Clin Oncol.* 2009;27(9):1419-1425. 7. Burger RA, et al. *N Engl J Med.* 2011;365:2473-2483. 8. Perren TJ, et al. *N Engl J Med.* 2011;365:2484-2496.

Multiple Lines of Chemotherapy Associated With Cumulative Toxicity While Remission Periods Decrease



Visual adapted from Giornelli GH. *Springerplus.* 2016;5(1):1197.
References in slide notes.
CA-125,cancer antigen 125; mPFS, median progression-free survival.

Advanced Ovarian Cancer Is Characterised By Multiple Relapses

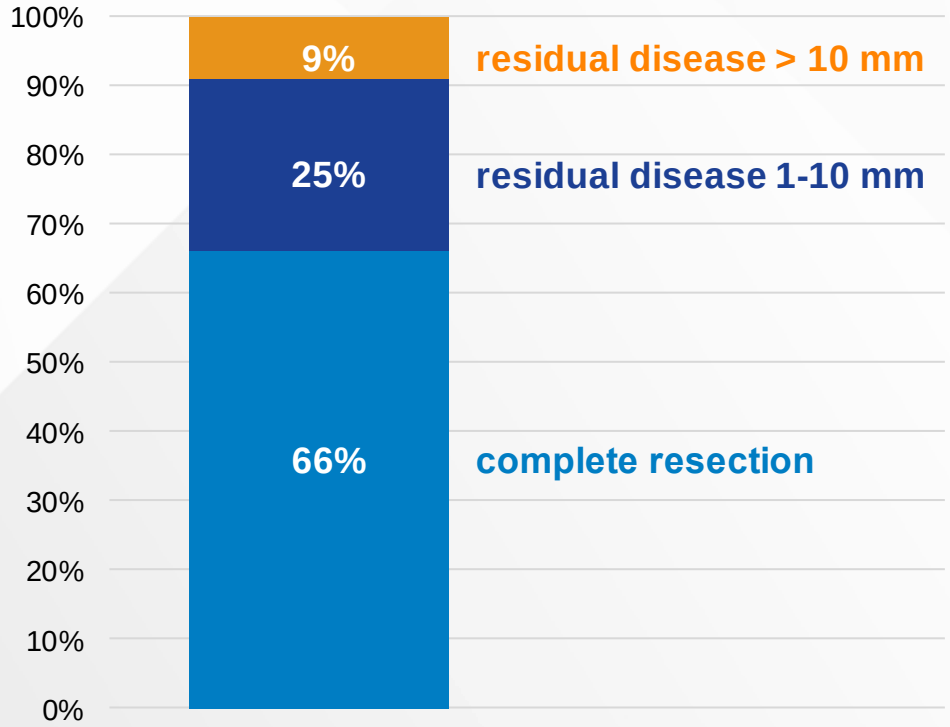
- Once the disease relapses, it is largely incurable
- First-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure

Giornelli GH. *Springerplus*. 2016;5(1):1197.

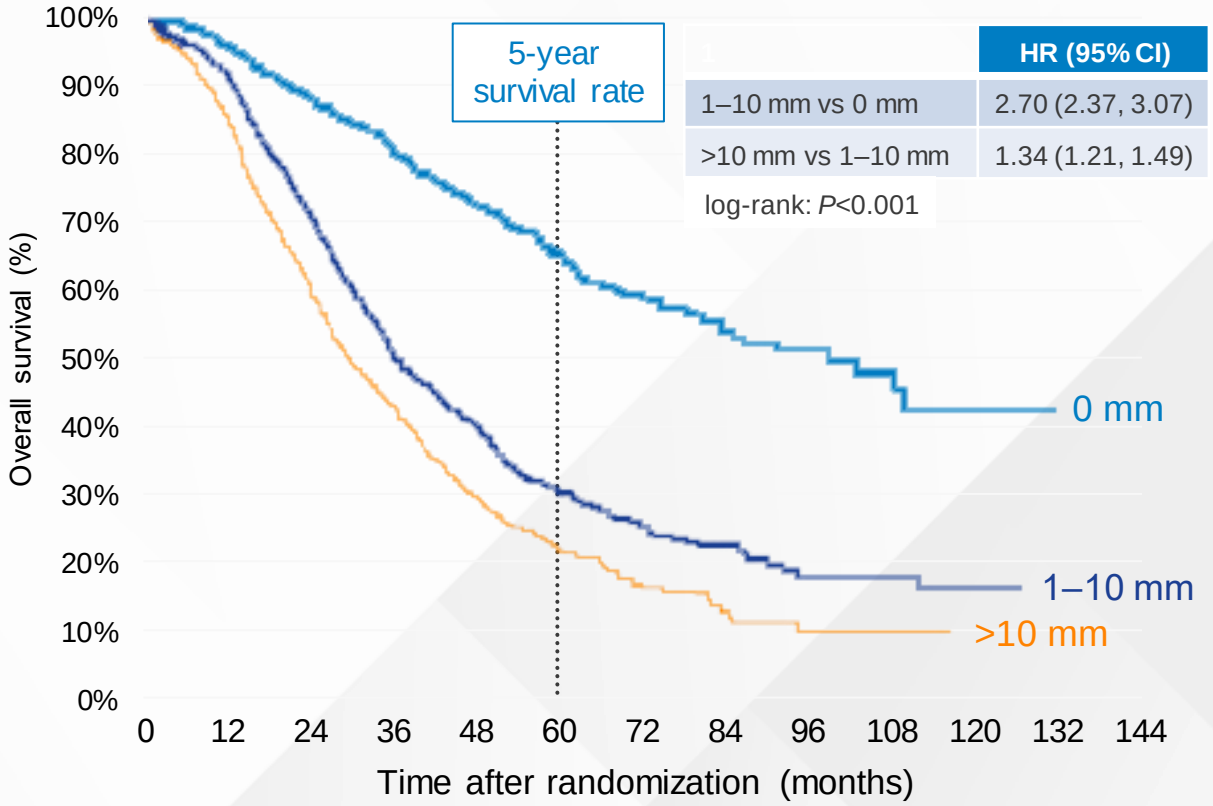
Impact of Postoperative Residual Disease on Outcome in Advanced Ovarian Cancer

Data from a meta-analysis of **three randomized frontline phase 3 trials** (AGO-OVAR 3, 5, and 7) with **3126 patients**[1]

FIGO IIIb–IV[2]



PFS after occurence[1]



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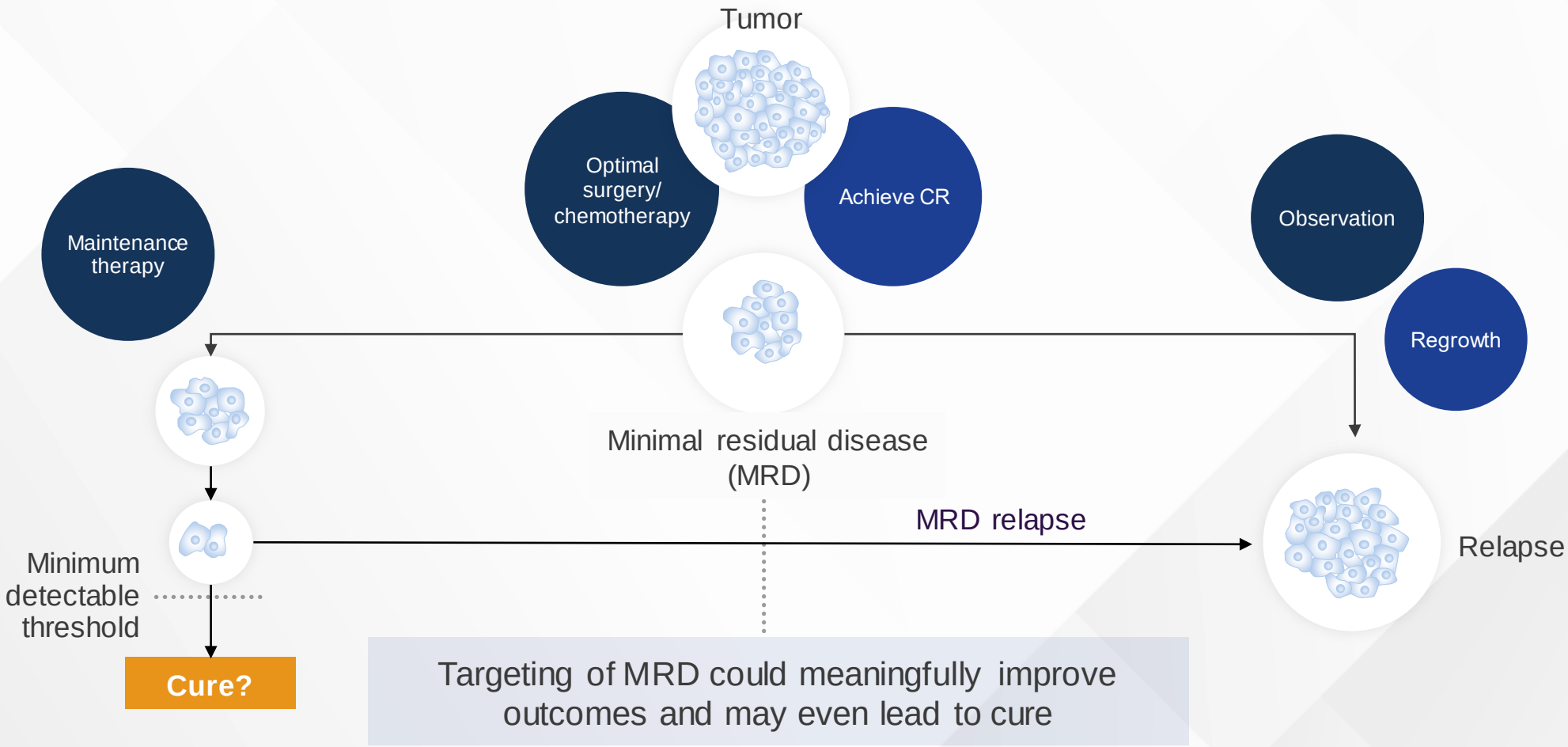
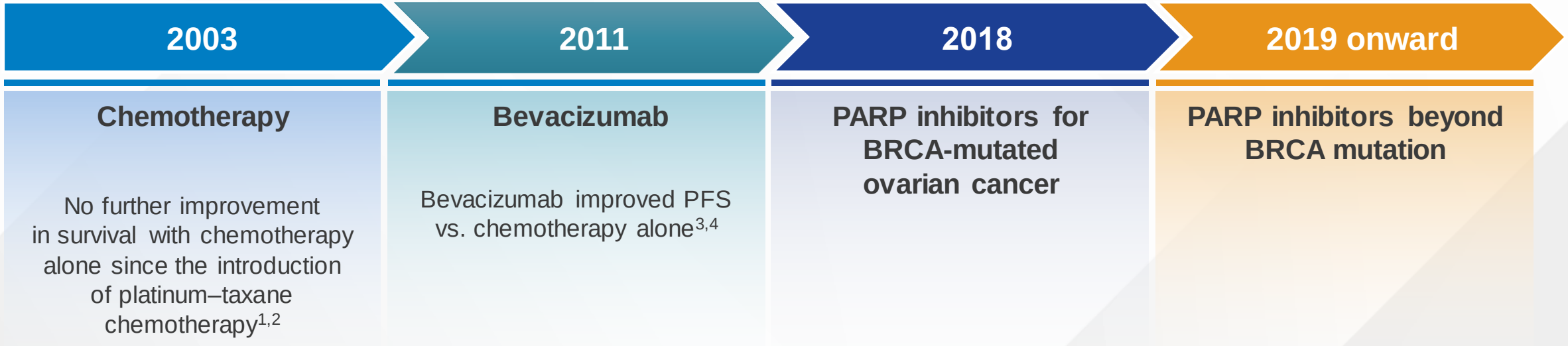
1. Du Bois, A et al. *Cancer.* 2009;115(6):1234-1244. 2. Heitz F, et al. *Gynecol Oncol.* 2016;141(2):264-270.
AGO-OVAR, Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom; CI, confidence interval;
FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; PFS, progression-free survival.

Treating Minimal Residual Disease: Aiming to Achieve Long-Term Disease Control



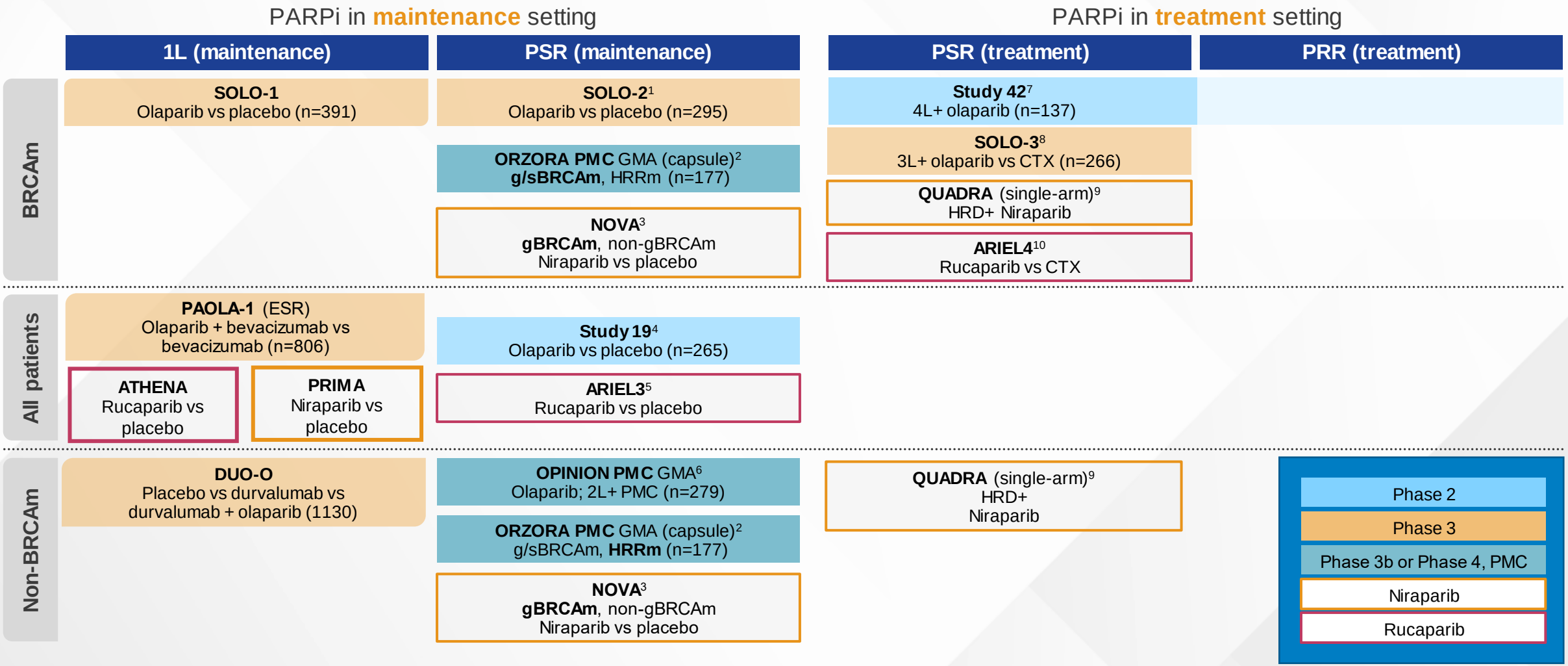
Luskin MR, et al. *Nat Rev Cancer.* 2018;18(4):255-263.
CR, complete response; MRD, minimal residual disease.

Significant Progress Has Been Made in the Management of Ovarian Cancer Over the Past Decade



1. McGuire WP, et al. *N Engl J Med.* 1996;334:1-6. 2. du Bois A, et al. *J Natl Cancer Inst.* 2003;95:1320-1329. 3. Burger RA, et al. *N Engl J Med.* 2011;365:2473-2483.
4. Perren TJ, et al. *N Engl J Med.* 2011;365:2484-2496.
BRCA, BRCA1 and/or BRCA2; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

Phase II/III Studies of PARP Inhibitors in Ovarian Cancer Management



1. Poveda A, et al. *Lancet Oncol*. 2021;22(5):620-631. 2. Pignata S, et al. *Gynecologic Oncol*. 2023;172:121-129. 3. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-2164. 4. Ledermann JA, et al. *Ther Adv Med Oncol*. 2019;11:1758835919849753. 5. Coleman RL, et al. *The Lancet* 2017;390:1949-1961. 6. Poveda A, et al. *Gynecol Oncol*. 2022;164(3):498.504. 7. Domchek SM, et al. *Gynecol Oncol*. 2016;140(2):199.203. 8. Penson RT, et al. *J Clin Oncol*. 2020;38(11):1164-1174. 9. Moore K, et al. *Lancet Oncol*. 2019;20(5):636-648. 10. Kristeleit R, et al. *Lancet Oncol* 2022;23(4):465-478. 11. Cadoo K, et al. *Gynecol Oncol*. 2022;166(3):425-431.

1/2/3/4L, first/second/third/fourth line; CTX, chemotherapy; GMA, Global Medical Affairs; g/sBRCAm, germline/somatic *BRCA1* and/or *BRCA2* mutation; HRD, homologous recombination deficiency; HRRm, homologous recombination repair gene mutation; OC, ovarian cancer; PARPi, poly(ADP-ribose) polymerase inhibitor; PMC, post-marketing commitment; PRR, platinum-resistant relapse(d); PSR, platinum-sensitive relapse(d).

Phase II/III Studies of PARP Inhibitors in Ovarian Cancer Management

PARPi in **maintenance** setting

PARPi in **treatment** setting

	1L (maintenance)	PSR (maintenance)	PSR (treatment)	PRR (treatment)
BRCAm	**SOLO-1** Olaparib vs placebo (n=391)	**SOLO-2**[1] Olaparib vs placebo (n=295)	**Study 42**[7] 4L+ olaparib (n=137)	
		ORZORA PMC GMA (capsule)[2] g/sBRCAm, HRRm (n=177)	**SOLO-3**[8] 3L+ olaparib vs CTX (n=266)	
		NOVA[3] **gBRCAm**, non-gBRCAm Niraparib vs placebo	**QUADRA** (single-arm)[9] HRD+	
			ARIEL4[10] Rucaparib vs CTX	
All patients	**PAOLA-1** (ESR) Olaparib + bevacizumab vs bevacizumab (n=806)	**Study 19**[4] Olaparib vs placebo (n=265)		
	PRIMA Niraparib vs placebo	**ARIEL3**[5] Rucaparib vs placebo		
Non-BRCAm	**ATHENA** Rucaparib vs placebo	**OPINION PMC** GMA[6] Olaparib; 2L+ PMC (n=279)	**QUADRA** (single-arm)[9] HRD+ Niraparib	
	DUO-O Placebo vs durvalumab vs durvalumab + olaparib (1130)	**ORZORA PMC** GMA (capsule)[2] g/sBRCAm, **HRRm** (n=177)		
		NOVA[3] **gBRCAm**, non-gBRCAm Niraparib vs placebo		

Phase 2

Phase 3

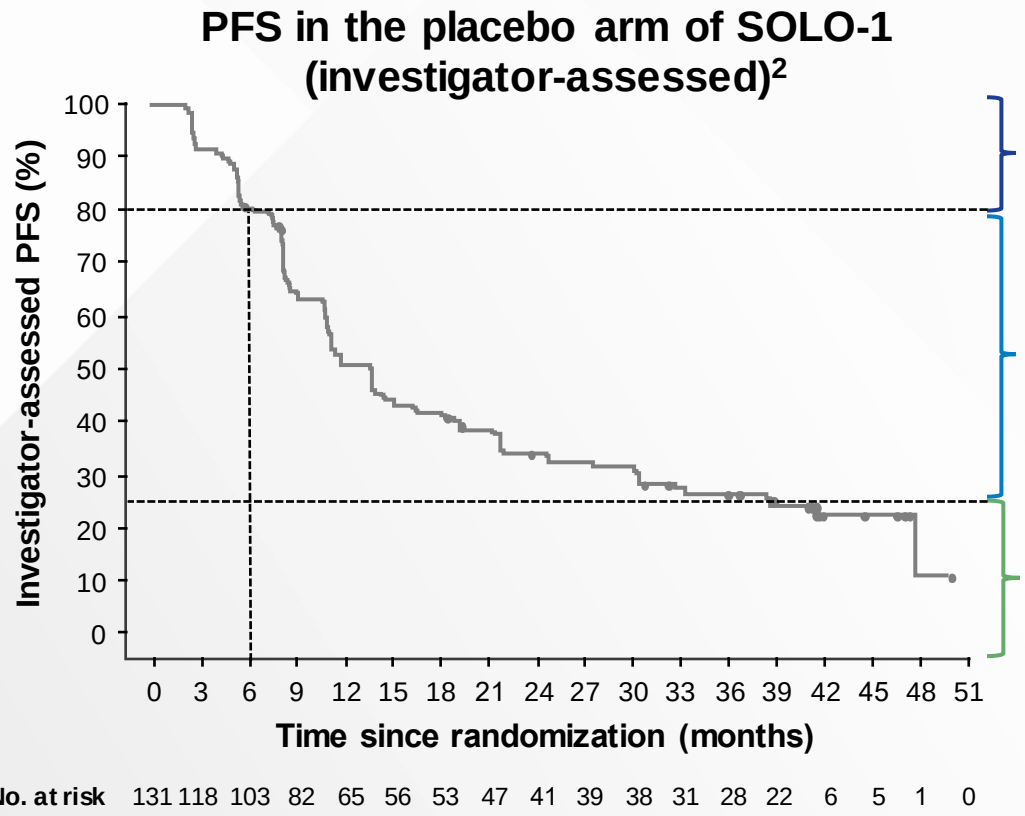
Phase 3b or Phase 4, PMC

Niraparib

Rucaparib

1. Poveda A, et al. *Lancet Oncol*. 2021;22(5):620-631. 2. Pignata S, et al. *Gynecologic Oncol*. 2023;172:121-129. 3. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-2164. 4. Ledermann JA, et al. *Ther Adv Med Oncol*. 2019;11:1758835919849753. 5. Coleman RL, et al. *The Lancet* 2017;390:1949-1961. 6. Poveda A, et al. *Gynecol Oncol*. 2022;164(3):498.504. 7. Domchek SM, et al. *Gynecol Oncol*. 2016;140(2):199.203. 8. Penson RT, et al. *J Clin Oncol*. 2020;38(11):1164-1174. 9. Moore K, et al. *Lancet Oncol*. 2019;20(5):636-648. 10. Kristeleit R, et al. *Lancet Oncol* 2022;23(4):465-478. 11. Cadoo K, et al. *Gynecol Oncol*. 2022;166(3):425-431.
1/2/3/4L, first/second/third/fourth line; CTX, chemotherapy; GMA, Global Medical Affairs; g/sBRCAm, germline/somatic *BRCA1* and/or *BRCA2* mutation; HRD, homologous recombination deficiency; HRRm, homologous recombination repair gene mutation; OC, ovarian cancer; PARPi, poly(ADP-ribose) polymerase inhibitor; PMC, post-marketing commitment; PRR, platinum-resistant relapse(d); PSR, platinum-sensitive relapse(d).

Earlier Introduction of PARP Inhibitors May Offer the Opportunity for a Greater Number of Patients to Benefit[1]



~20% relapse within 6 months

~55% relapse after 6 months

~25% long-term remission

Platinum-resistant: Ineligible for PARP inhibitor maintenance at relapse[3]

Platinum-sensitive: ~40% of patients fail to respond to subsequent platinum therapy[4,5] and are ineligible for PARP inhibitor maintenance in the second-line setting[3]

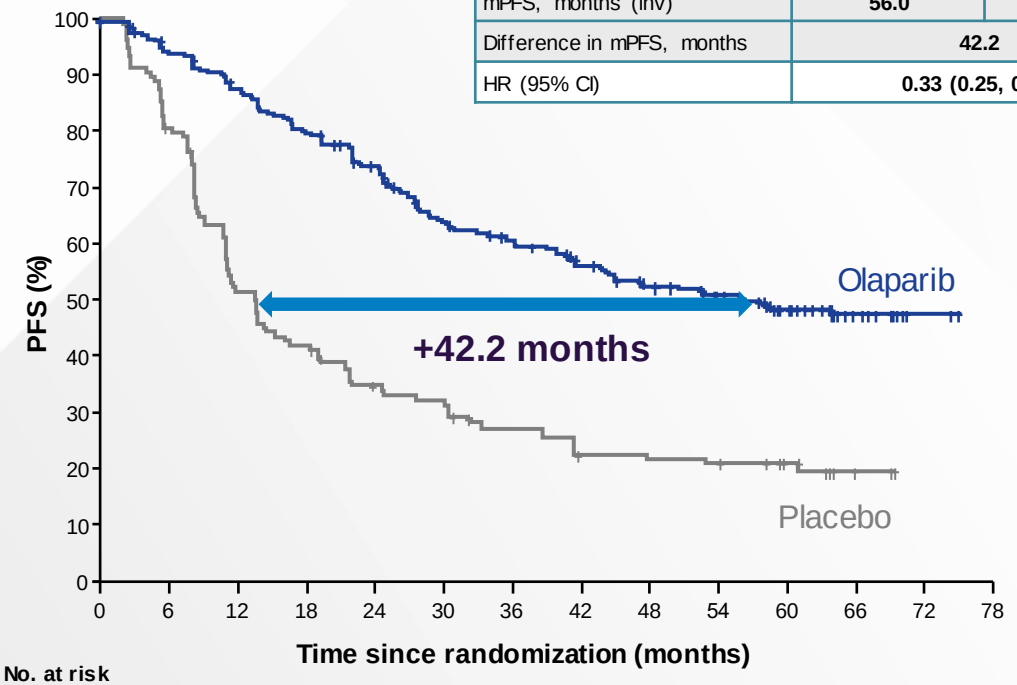
Long-term remission (cure?): Ultimate goal of multimodality first-line therapy is to cure patients with advanced ovarian cancer[1]

1. Miller RE, et al. *Future Oncol.* 2019;15(16):1845-1853. 2. Moore K, et al. *N Engl J Med.* 2018;379:2495-2505. 3. LYNPARZA (olaparib). Prescribing Information. AstraZeneca; 2023. 4. Bruchim I, et al. *Eur J Obstet Gynecol Reprod Biol.* 2013;166(1):94-98. 5. Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045.
PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

The PFS Benefit Shown in SOLO-1 Compared With SOLO-2 Highlights the Importance of Introducing PARPi as Early as Possible

SOLO-1[1,2]

	Olaparib 1L	Placebo
Events, N (%)	**118 (45)**	**100 (76)**
mPFS, months (inv)	**56.0**	**13.8**
Difference in mPFS, months	**42.2**	
HR (95% CI)	**0.33 (0.25, 0.43)**	

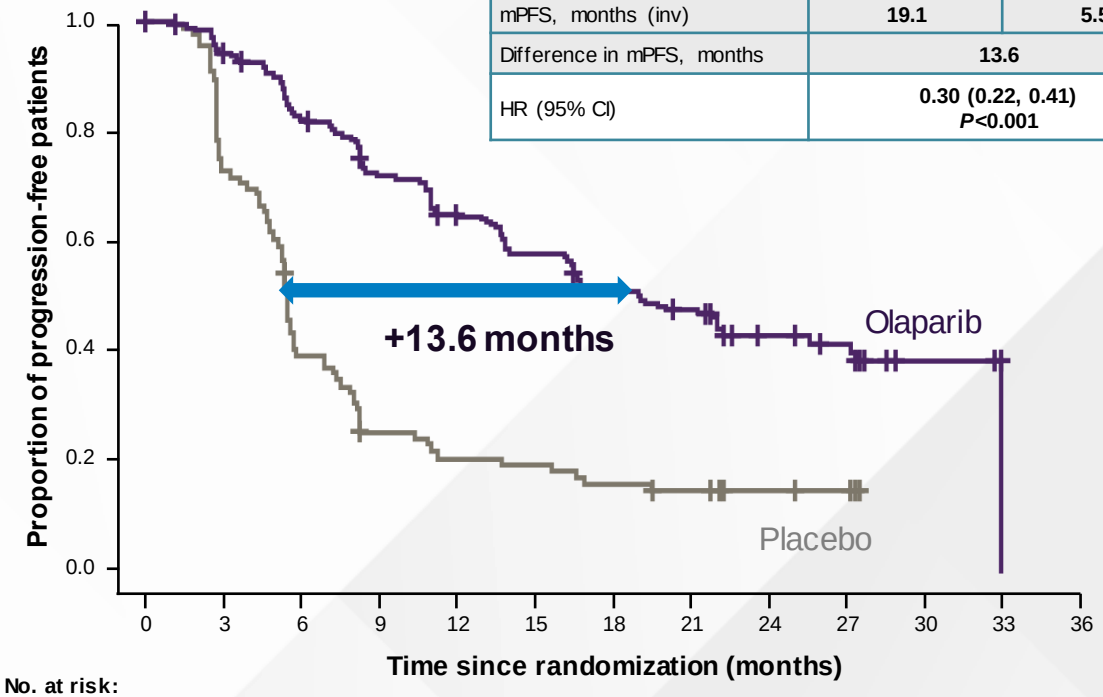


No. at risk

Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	0

SOLO-2[2,3]

	Olaparib PSR	Placebo
Events, N (%)	**107 (54.6)**	**80 (80.8)**
mPFS, months (inv)	**19.1**	**5.5**
Difference in mPFS, months	**13.6**	
HR (95% CI)	**0.30 (0.22, 0.41)** ***P*<0.001**	



No. at risk:

Olaparib	196	182	156	134	118	104	89	82	32	29	3	2	0
Placebo	99	70	37	22	18	17	14	12	7	6	0	0	0

Cross-trial comparisons should be done with precaution as such trials differed in design, size, time period of recruitment, location of study sites, etc.

1. Banerjee S, et al. *Lancet Oncol.* 2021;22(12):1721-1731. 2. Lynparza. Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. 3. Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-1284.

1L, first-line; CI, confidence interval; HR, hazard ratio; inv, investigator-assessed; mPFS, median progression-free survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PSR, platinum-sensitive relapsed.

Clinical Data for PARP Inhibitors as Maintenance Therapy for Newly-Diagnosed Advanced Ovarian Cancer

Significant Progress Has Been Made in the First-Line Management of Ovarian Cancer Over the Past Decade

2003

Chemotherapy

No further improvement in survival with chemotherapy alone since the introduction of platinum–taxane chemotherapy[1,2]

2011

Paradigm shift 1:
Bevacizumab

Bevacizumab improved PFS versus chemotherapy alone[3,4]

2018

Paradigm shift 2:
PARP inhibitors for BRCA-mutated ovarian cancer

Olaparib	SOLO-1[5] *NCT01844986*

2019–2022

Paradigm shift 3:
PARP inhibitors beyond BRCA mutation

Olaparib + bevacizumab	PAOLA-1[6] *NCT02477644*
Niraparib	PRIMA[7] *NCT02655016*
Rucaparib[a]	ATHENA-mono[8] *NCT03522246*

Several studies with PARP inhibitor maintenance for newly-diagnosed advanced ovarian cancer[5–8]

[a]Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.

1. McGuire WP, et al. *N Engl J Med.* 1996;334:1-6. 2. du Bois A, et al. *J Natl Cancer Inst.* 2003;95(17):1320-1329. 3. Burger RA, et al. *N Engl J Med.* 2011;365:2473-2483. 4. Perren TJ, et al. *N Engl J Med.* 2011;365:2484-2496. 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01844986 (Accessed March 2022). 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477644 (Accessed March 2022). 7. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016 (Accessed March 2022). 8. Monk JM, et al. *J Clin Oncol.* 2022;40(34):3952-3964.
BRCA, *BRCA*1 and/or *BRCA*2; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

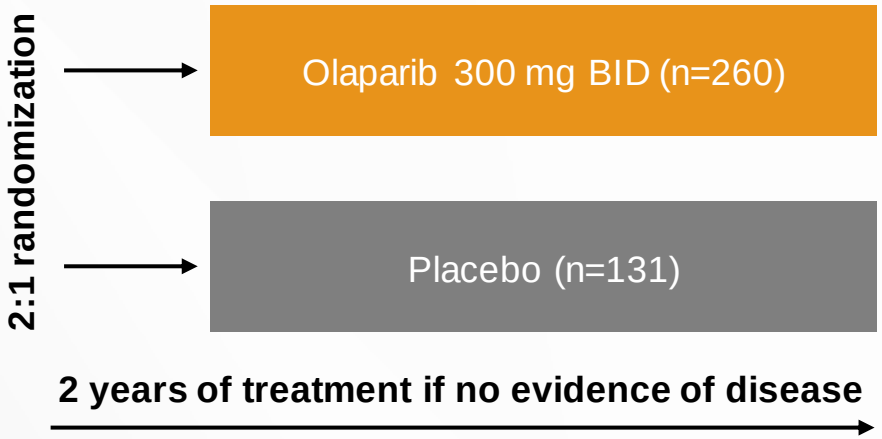
SOLO-1: Maintenance Olaparib for Patients With Newly-Diagnosed BRCAm Advanced Ovarian Cancer

Patient population

- HGSOC or HGEOC
- FIGO Stage III or IV
- Germline or somatic BRCA mutation
- ECOG 0–1
- Cytoreductive surgery
- CR or PR after platinum chemotherapy

Stratification

- Response to platinum chemotherapy



Primary objective

- Investigator-assessed PFS[a]

Secondary efficacy objectives

- PFS by BICR
- Time to second progression or death
- OS
- TFST
- TSST
- HRQoL

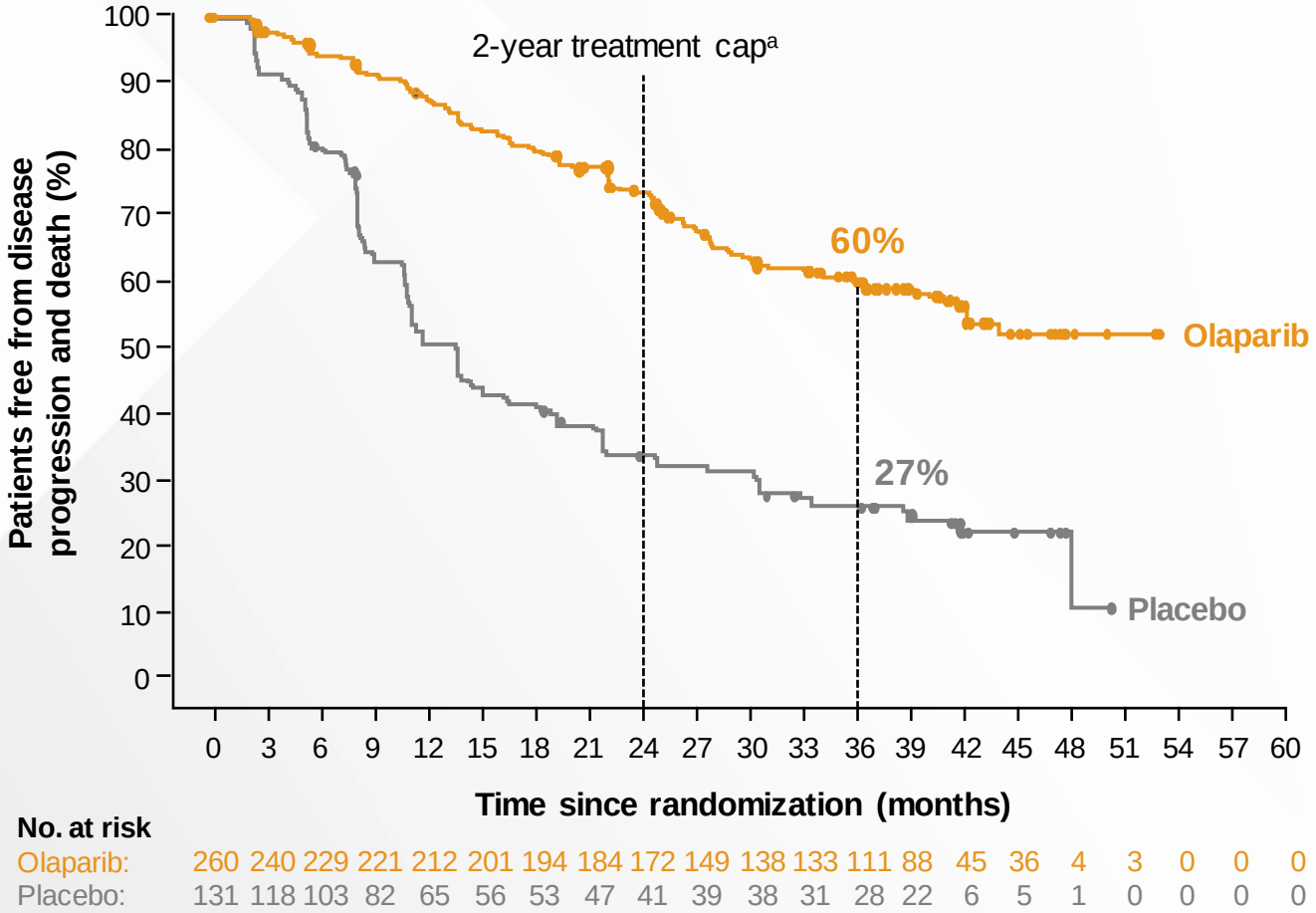
Safety and tolerability

[a]Modified Response Evaluation Criteria in Solid Tumors version 1.1

Moore K, et al. *N Engl J Med.* 2018;379:2495-2505.

BICR, blinded independent central review; BID, twice daily; BRCAm, BRCA1- and/or BRCA2-mutated; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PR, partial response; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

SOLO-1: Olaparib Reduced the Risk of Progression or Death by 70% Versus Placebo



	Olaparib (n=260)	Placebo (n=131)
Events (%) [50.6% maturity]	**102 (39.2)**	**96 (73.3)**
Median PFS, months	**NR**	**13.8**
HR (95% CI)	**0.30 (0.23, 0.41)**	
	***P*<0.0001**	

Median follow-up for PFS:

Olaparib 40.7 months

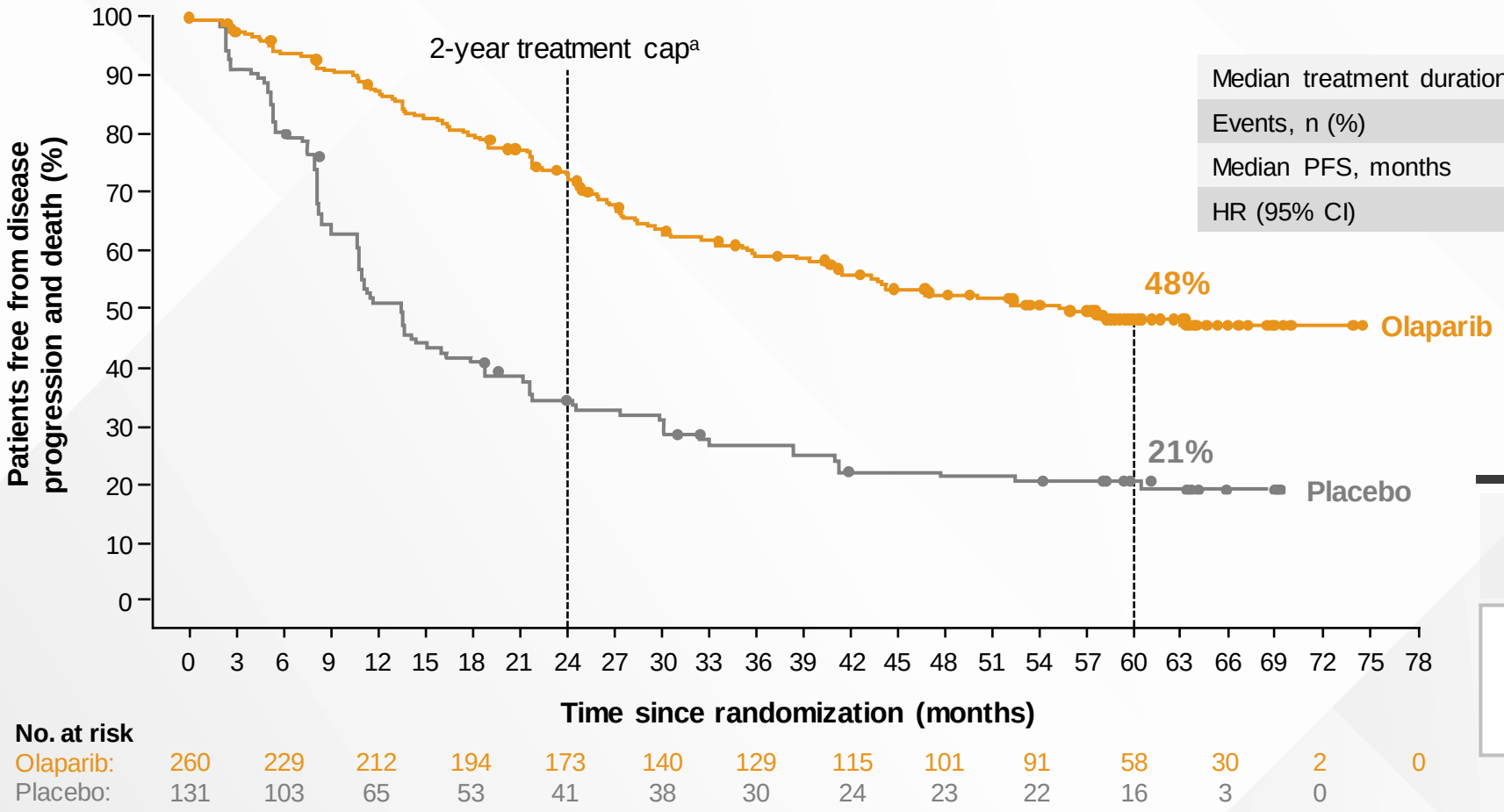
Placebo 41.2 months

[a]Patients who had no evidence of disease at 2 years stopped receiving the trial intervention; patients who had a partial response at 2 years were permitted to continue receiving the trial intervention in a blinded manner; 13 patients (all in the olaparib arm) continued study treatment past 2 years.

Moore K, et al. *N Engl J Med.* 2018;379:2495-2505.

CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

SOLO-1: PFS Benefit of Maintenance Olaparib Was Sustained Beyond the End of Treatment



	Olaparib (n=260)	Placebo (n=131)
Median treatment duration, months	24.6	13.9
Events, n (%)	118 (45)	100 (76)
Median PFS, months	56.0	13.8
HR (95% CI)	0.33 (0.25, 0.43)	

No. at risk

Olaparib:	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo:	131	103	65	53	41	38	30	24	23	22	16	3	0	

Median PFS difference for olaparib vs placebo: 42.2 months

Median follow-up for PFS:

Olaparib	Placebo
4.8 years	5.0 years

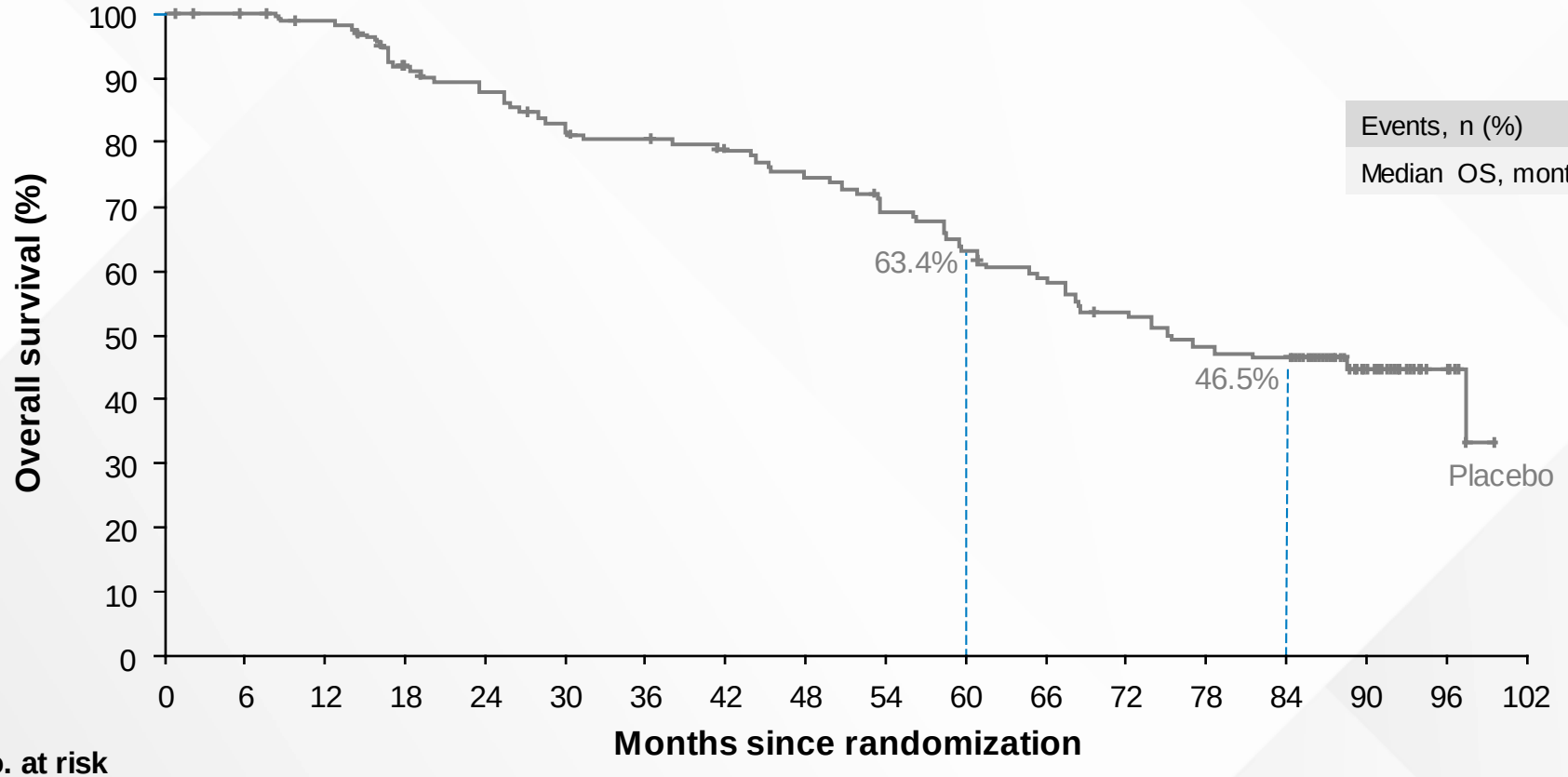
Investigator-assessed by modified RECIST v1.1.

[a]Patients who had no evidence of disease at 2 years stopped receiving the trial intervention; patients who had a partial response at 2 years were permitted to continue receiving the trial intervention in a blinded manner; 13 patients (all in the olaparib arm) continued study treatment past 2 years.

Banerjee S, et al. ESMO Virtual Congress 2020. Abstract 811MO.

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours.

SOLO-1: Descriptive OS Analysis



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

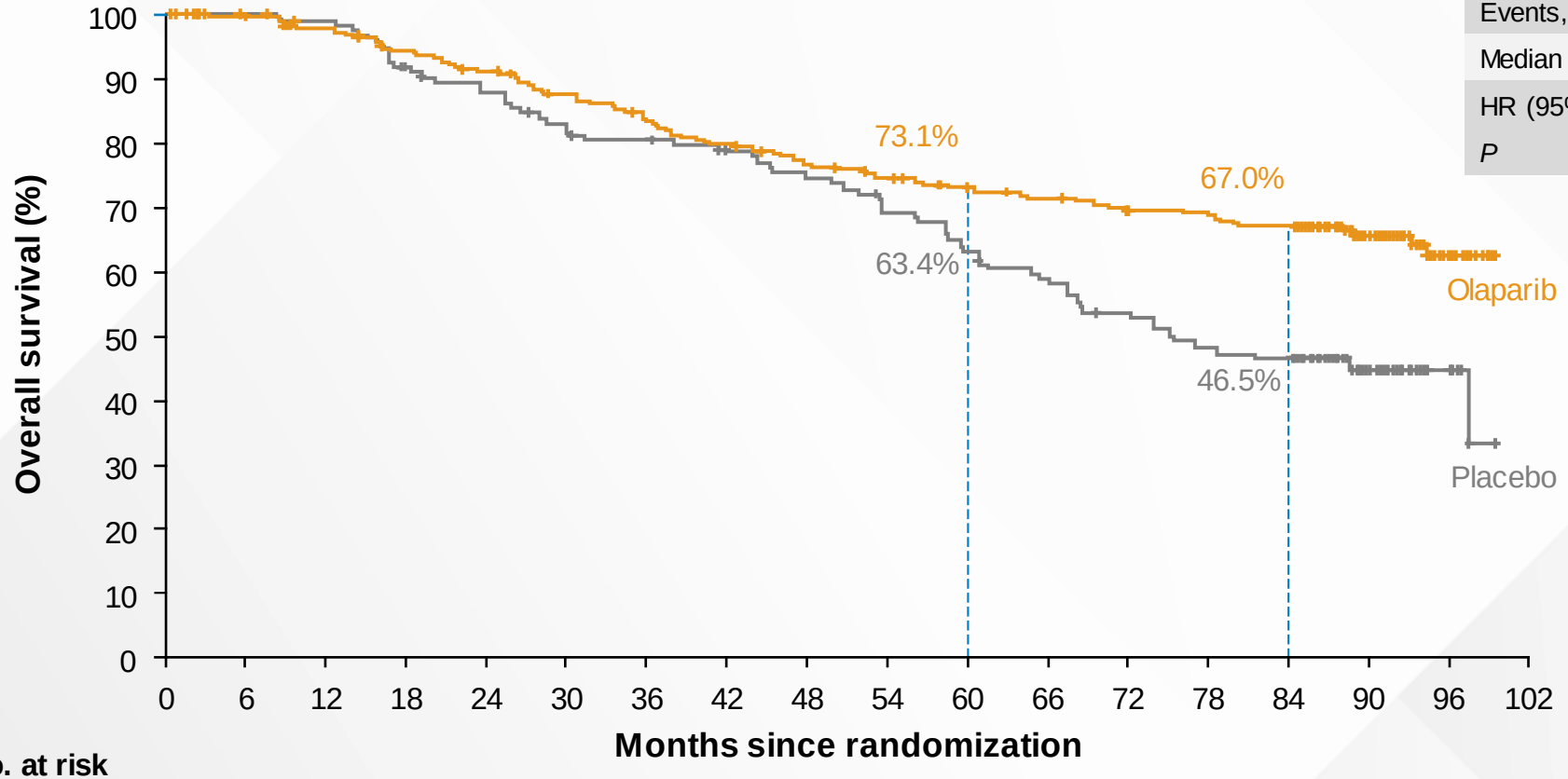
No. at risk

Placebo	131	128	125	114	108	100	97	92	87	80	73	67	60	54	52	21	6	0

DiSilvestro P, et al. *J Clin Oncol*. 2023;41(3):609-617.
OS, overall survival.

SOLO-1: Maintenance Olaparib Provided a Clinically Meaningful OS Benefit

	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**
HR (95% CI)	**0.55** (0.40–0.76)	
P	0.0004[a]	



No. at risk

Olaparib	260	252	246	236	227	214	203	194	185	177	170	165	159	157	153	79	21	0
Placebo	131	128	125	114	108	100	97	92	87	80	73	67	60	54	52	21	6	0

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

[a]*P*<0.0001 required to declare statistical significance.

DiSilvestro P, et al. *J Clin Oncol*. 2023;41(3):609-617.

CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PARP, poly(ADP-ribose) polymerase.

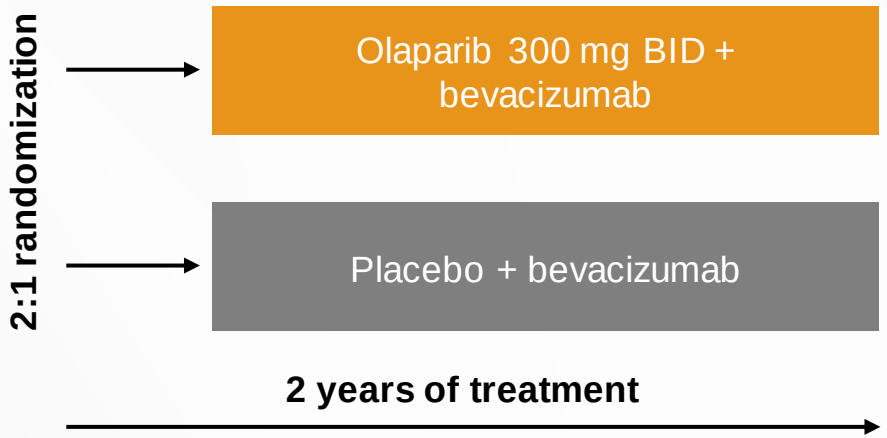
PAOLA-1: Olaparib Plus Bevacizumab as Maintenance Therapy in Patients With Newly-Diagnosed Advanced Ovarian Cancer[1]

Key inclusion criteria

- Newly-diagnosed, FIGO Stage III–IV HGSOC and HGEOC[a]
- PDS or IDS
- ≥2 cycles of bevacizumab[b]
- NED/CR/PR

Stratification

- Tumor BRCA status[c]
- First-line treatment outcome[d]



Primary objective

- Investigator-assessed PFS[a]

Secondary efficacy objectives

- PFS2, OS, TFST, TSST, HRQoL

Safety and tolerability

Exploratory PFS analyses[2]

Higher-risk patients:

- FIGO Stage III patients with PDS and residual disease or who had received NAC
- FIGO Stage IV patients

Lower-risk patients:

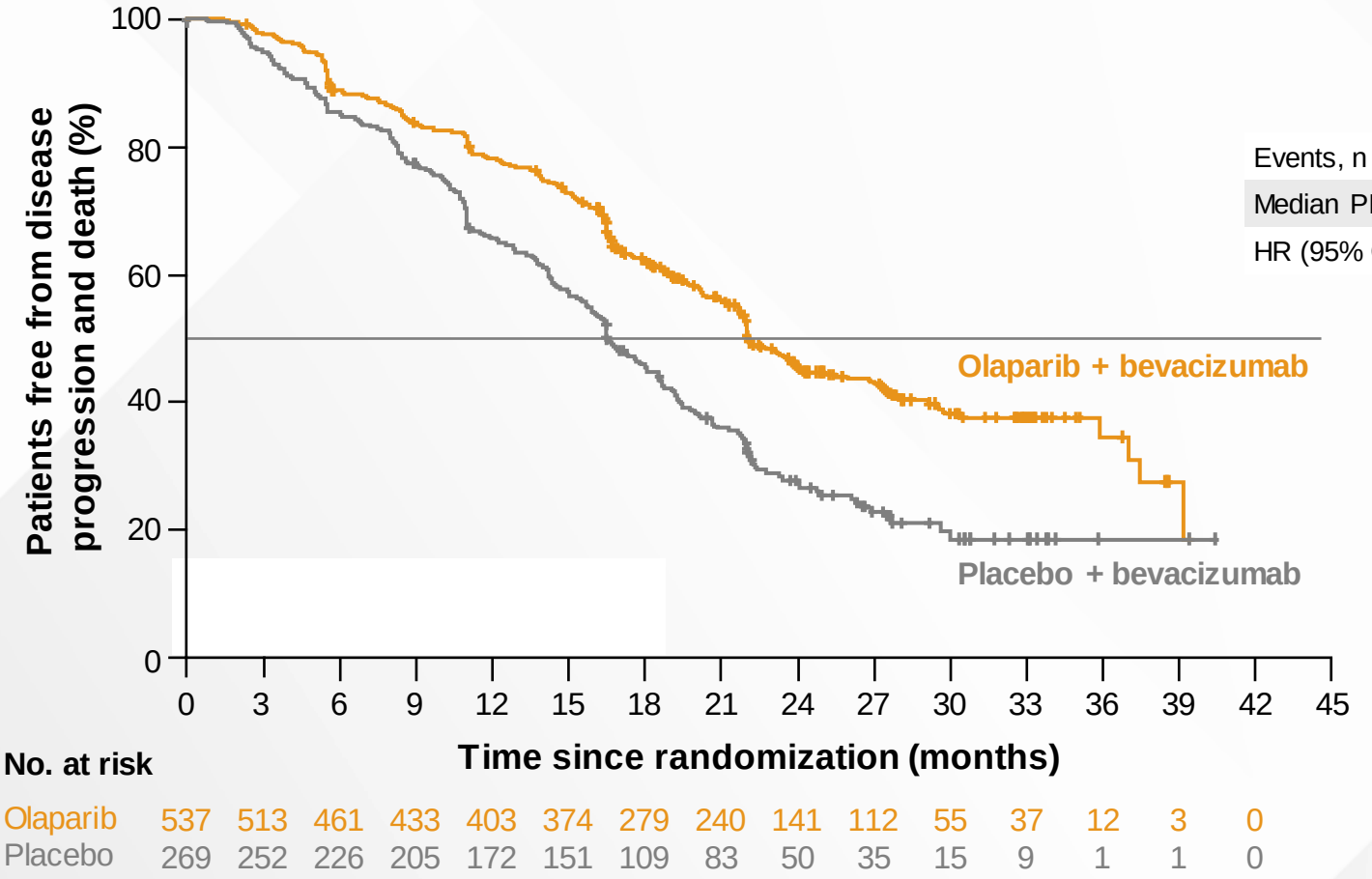
- FIGO Stage III patients with PDS with no residual disease

[a]Includes patients with primary peritoneal and/or fallopian tube cancer; patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation; [b]Bevacizumab 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; [c]By central labs; [d]According to timing of surgery and NED/CR/PR

1. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. 2. Harter P, et al. *Int J Gynecol Cancer.* 2020;30(suppl 3):A13-A14.

BID, twice daily; BRCA, *BRCA1* and/or *BRCA2*; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRQoL, health-related quality of life; IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; NED, no evidence of disease; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; PFS2, time to second progression or death; PR, partial response; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

PAOLA-1: Olaparib Plus Bevacizumab Significantly Improved PFS vs Bevacizumab in the ITT Population[1]



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

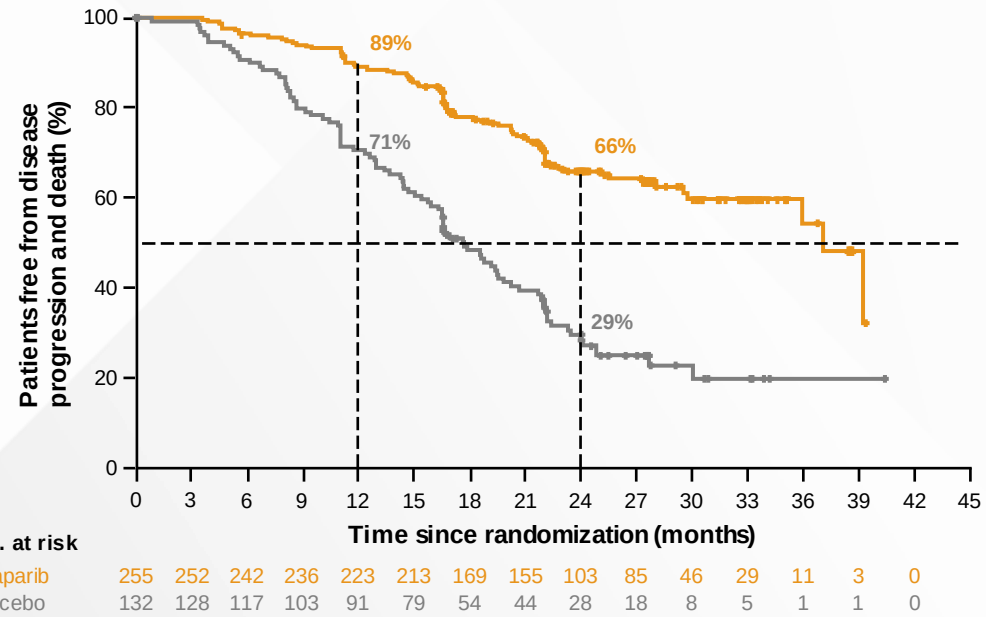
Hard to interpret without an olaparib monotherapy arm…

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

1. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. 2. Ray-Coquard I, et al. ESMO Congress 2019. Abstract LBA2_PR.
HR, hazard ratio; ITT, intent to treat.

PAOLA-1: Prespecified Subgroup Analysis Showed Substantial PFS Benefit in HRD-Positive (Including tBRCAm) Patients

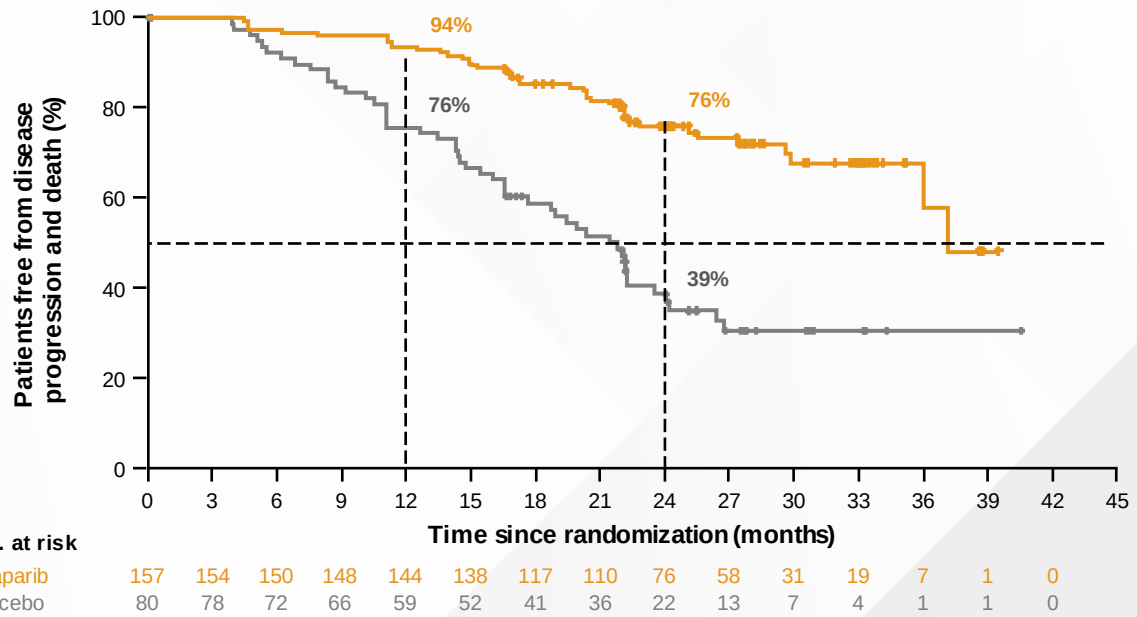
HRD-positive



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

	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	**87 (34)**	**92 (70)**
Median PFS, months (inv)	**37.2**	**17.7**
HR (95% CI)	**0.33 (0.25, 0.45)**	

tBRCAm



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

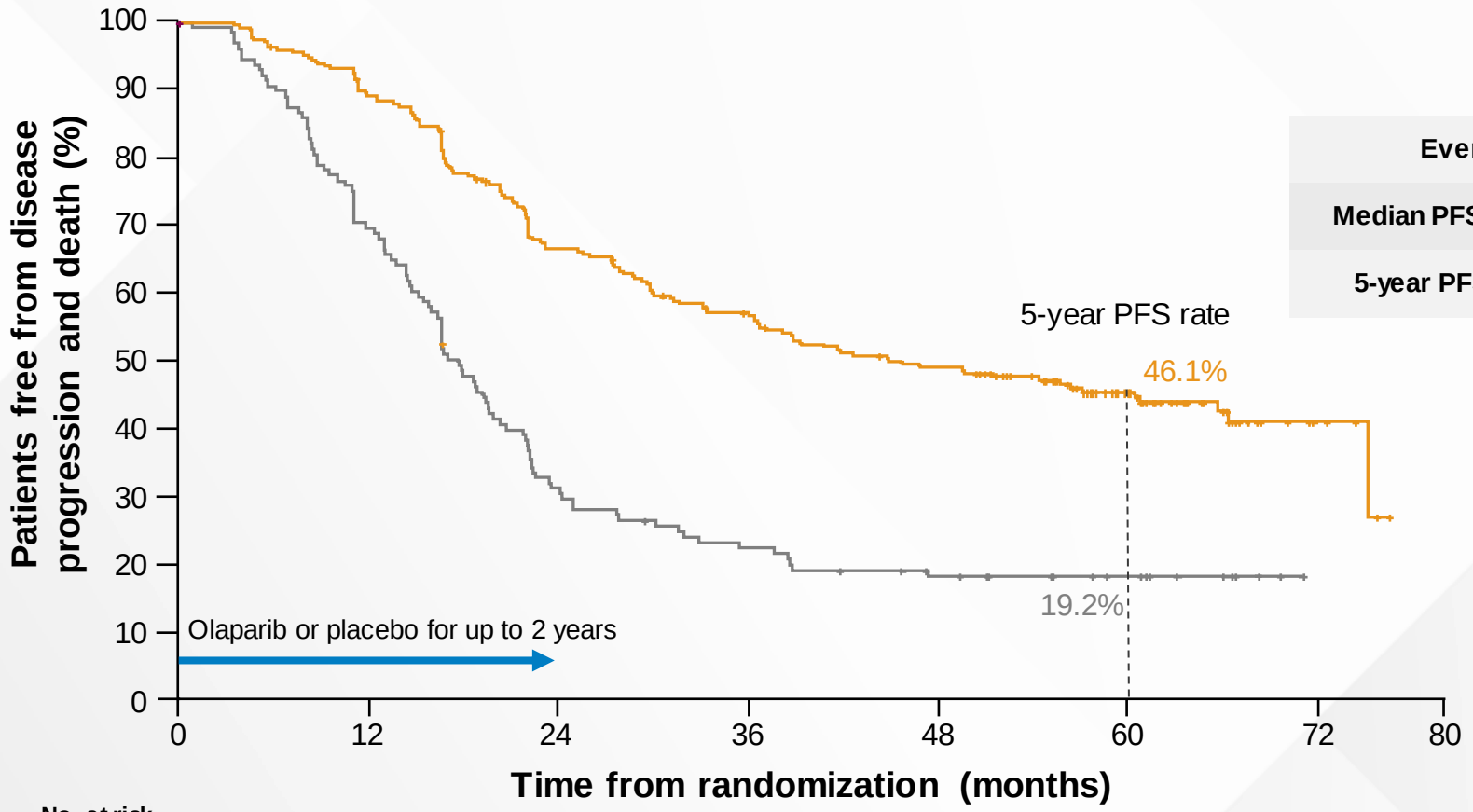
	Olaparib + bevacizumab (n=157)	Placebo + bevacizumab (n=80)
Events, n (%)	**41 (26)**	**49 (61)**
Median PFS, months (inv)	**37.2**	**21.7**
HR (95% CI)	**0.31 (0.20, 0.47)**	

AXIS Medical Education

Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; inv, investigator-assessed; PFS, progression-free survival; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

PAOLA-1: Updated PFS at 5 Years: HRD-Positive Population[a]



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

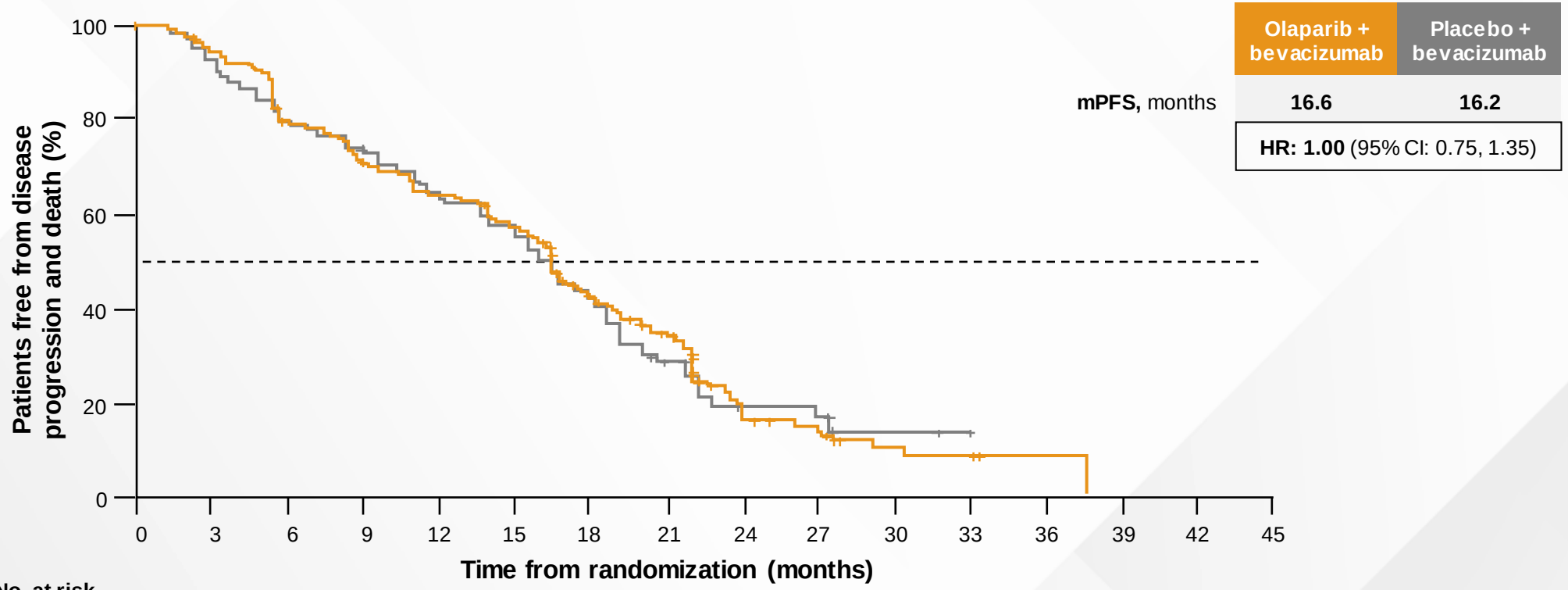
HR: 0.41 (95% CI: 0.32–0.54)

No. at risk

Olaparib + bevacizumab	255	252	242	236	223	214	194	183	165	162	147	143	138	127	123	119	117	112	103	79	63	40	31	8	5	3	0
Placebo + bevacizumab	132	129	118	103	91	79	62	52	41	37	34	30	29	25	24	24	21	20	19	15	13	8	6	2	0		

[a]Descriptive analysis; PFS by investigator-assessment (modified RECIST v1.1).
Ray-Coquard I, et al. ESMO Annual Meeting 2022. Abstract #LBA29.
CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; PFS, progression-free survival.

PAOLA-1: Olaparib plus Bevacizumab Demonstrated No Benefit vs Bevacizumab in the HRD-negative Population



	Olaparib + bevacizumab	Placebo + bevacizumab
mPFS, months	**16.6**	**16.2**

HR: 1.00 (95% CI: 0.75, 1.35)

No. at risk

Olaparib	192	175	145	128	115	102	67	49	20	13	6	5	1	0
Placebo	85	79	68	63	52	47	34	20	8	8	3	2	0	

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; mPFS, median progression-free survival.

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

PRIMA: Maintenance Niraparib for Patients With Newly-Diagnosed Ovarian Cancer, Regardless of BRCAm Status

Key inclusion criteria

- FIGO Stage III–IV HGSOC or HGEOC[a]
- Tissue for HRD testing required at screening (Myriad myChoice®)
- CR or PR (<2 cm[b]) and normalization of CA-125 levels[c,2]

Key exclusion criteria

- Stage III disease with complete cytoreduction after PDS

2:1 randomization

Niraparib

Placebo

Stratification

- CR or PR
- NACT
- HRD-positive or HRD-negative/unknown

Body weight ≥77 kg and platelets ≥150,000/μL started with 300 mg QD

Body weight <77 kg and/or platelets <150,000/μL started with 200 mg QD

35% of patients received a modified starting dose after a protocol change; of these, 72% received 200 mg QD[3]; initial dose for everyone regardless of weight or platelets was 300 mg/day

3 years treatment if no evidence of disease

Primary endpoint

- PFS (BICR)

Secondary endpoints

- OS
- PFS2
- TFST
- PRO
- Safety

Hierarchical PFS testing

- Patients with HRD-positive disease, then ITT population

Patients were treated with niraparib or placebo once daily for 36 months or until disease progression.

[a]Includes patients with primary peritoneal and/or fallopian tube cancer; [b]Based on protocol modification; [c]Normal or >90% decrease in CA-125 with front-line treatment.

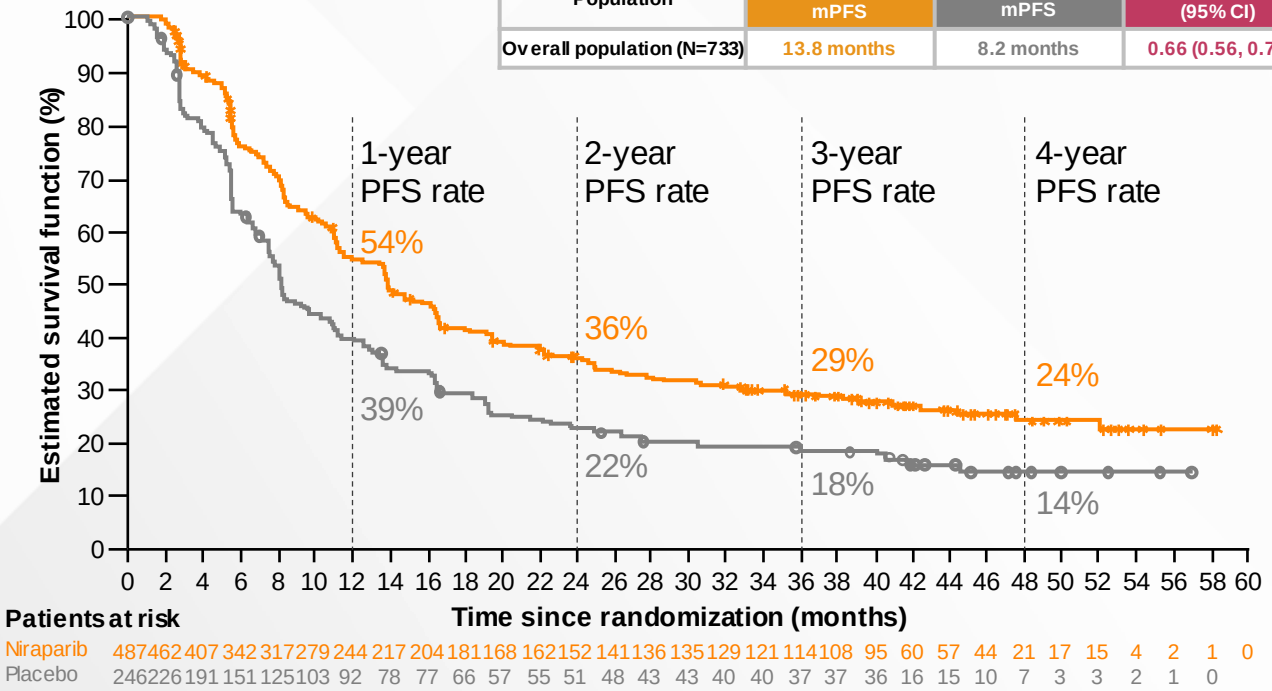
1. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016. 3. Mirza MR, et al. ASCO Virtual Scientific Program 2020. Abstract 6050.

BICR, blinded independent central review; BRCAm, *BRCA1* and/or *BRCA2* mutation; CA-125, cancer antigen 125; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; ITT, intention-to-treat; NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; PFS2, time to progression on subsequent therapy; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy.

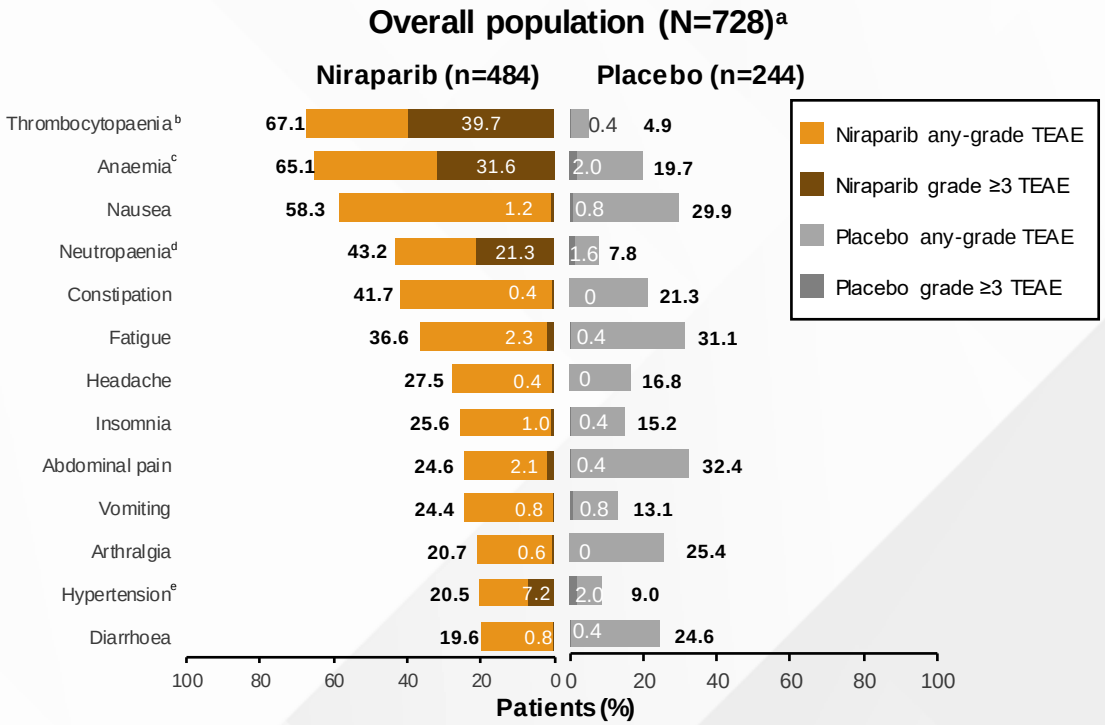
PRIMA: Niraparib Maintenance Therapy Significantly Improved PFS vs Placebo in the Overall Population

Investigator-assessed PFS in the overall population

Population	Niraparib mPFS	Placebo mPFS	Hazard ratio (95% CI)
Overall population (N=733)	13.8 months	8.2 months	0.66 (0.56, 0.79)



TEAEs reported in ≥20% of patients



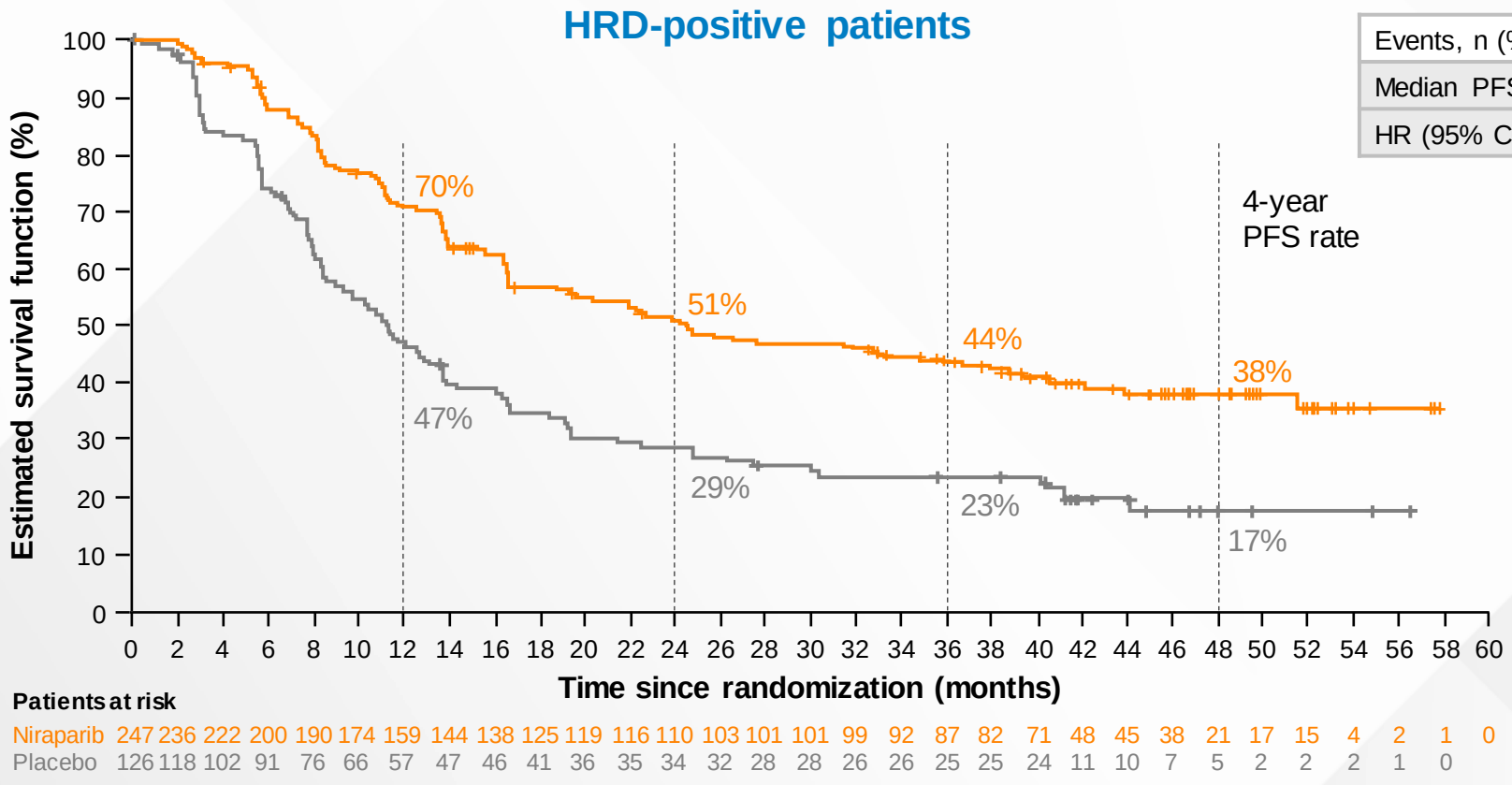
- Niraparib reduced the risk of progression or death by 34% versus placebo
- Adverse event findings were consistent with the primary analysis, with no new safety signals

[a]Patients who received ≥1 dose of study treatment; [b]Includes thrombocytopaenia and platelet count decreased; [c]Includes anaemia, haemoglobin decreased, red blood cell decreased, haematocrit decreased and macrocytic anaemia; [d]Includes neutropaenia, neutrophil count decreased, febrile neutropaenia and neutropenic sepsis; [e]Includes hypertension, blood pressure increased and blood pressure fluctuation.

Gonzales-Martin A, et al. ESMO Annual Meeting 2022. Abstract #530P.

CI, confidence interval; mPFS, median progression-free survival; TEAE, treatment-emergent adverse event.

PRIMA: Niraparib Maintenance Therapy Significantly Improved PFS vs Placebo in the HRD-Positive Population



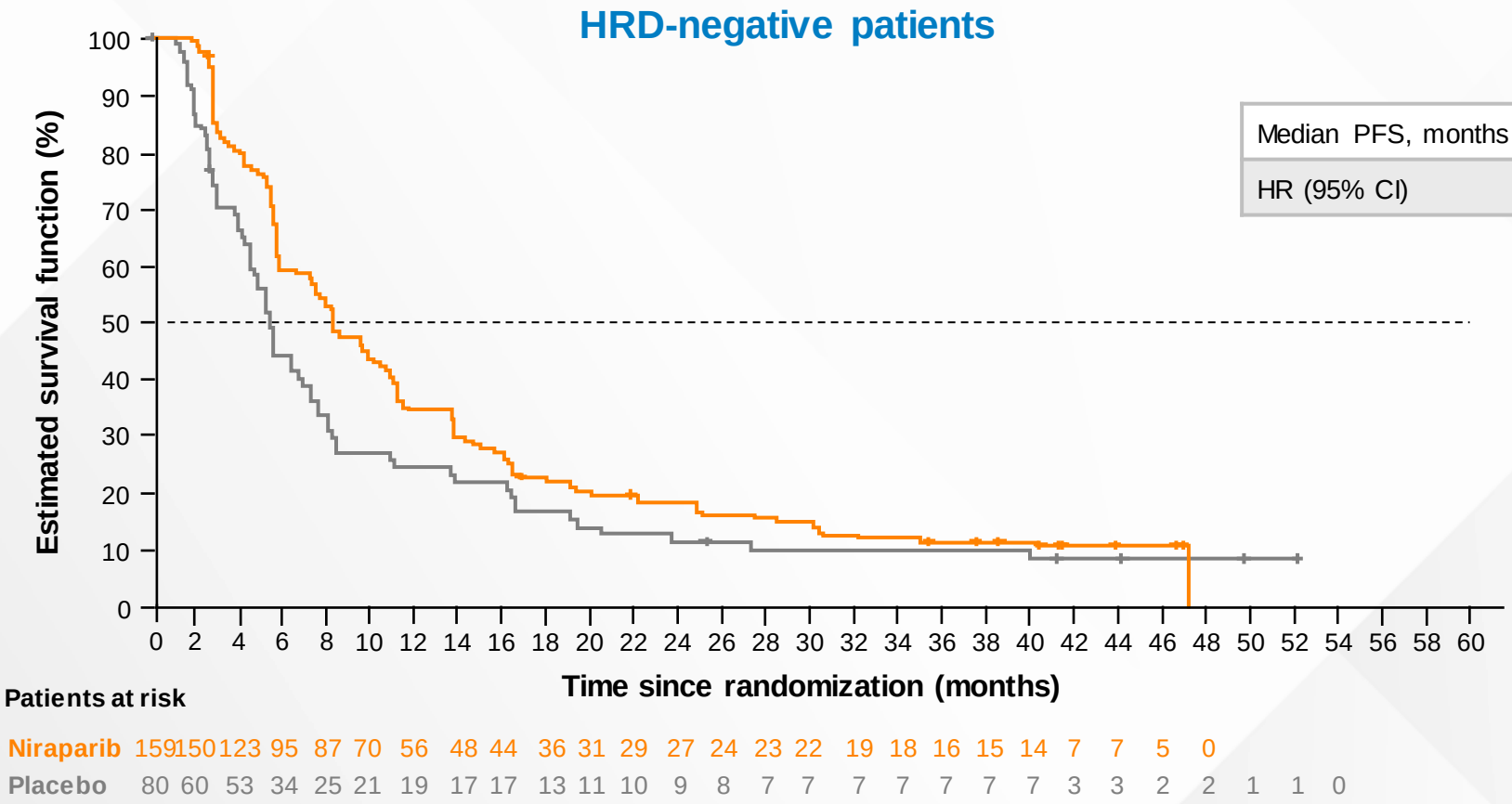
	Niraparib (n=152)	Placebo (n=71)
Events, n (%)	49 (32.2)	40 (56.3)
Median PFS, months	24.5	11.2
HR (95% CI)	**0.52 (0.40, 0.68)**	
	***P*<0.001**	

Median duration of follow-up: 3.5 years

Gonzales-Martin A, et al. ESMO Annual Meeting 2022. Abstract #530P.

CI, confidence interval; HR, hazard ratio; HRD; homologous recombination deficiency; PFS, progression-free survival

PRIMA: Niraparib Maintenance Therapy Demonstrated Limited PFS Benefit vs Placebo in the HRD-Negative Population



	Niraparib (n=152)	Placebo (n=71)
Median PFS, months	8.4	5.4
HR (95% CI)	**0.65 (0.49, 0.87)**	

Gonzales-Martin A, et al. ESMO Annual Meeting 2022. Abstract #530P.

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; PFS, progression-free survival.

DUO-O Study Design

The continuing saga of missing study arms...

Run-in phase

CTx cycle 1*

Patients

- Newly diagnosed FIGO stage III–IV high-grade epithelial OC
- No prior systemic therapy for OC
- PARP inhibitor/ immune-mediated therapy naïve
- Primary debulking or planned interval debulking surgery
- Non-tBRCAm

R
1:1:1

Stratified by:

- Timing and outcomes of cytoreductive surgery
- Geographical region

	Chemotherapy phase	Maintenance phase
Arm 1 PC + bev	**CTx**† + **bevacizumab** + **durvalumab placebo**	**Bevacizumab** total 15 months + **durvalumab placebo** total 24 months + **olaparib placebo** total 24 months
Arm 2 PC + bev + durva	**CTx**† + **bevacizumab** + **durvalumab**	**Bevacizumab** total 15 months + **durvalumab** total 24 months + **olaparib placebo** total 24 months
Arm 3 PC + bev + durva + ola	**CTx**† + **bevacizumab** + **durvalumab**	**Bevacizumab** total 15 months + **durvalumab** total 24 months + **olaparib** total 24 months

Endpoints

Primary endpoints

- PFS (RECIST per investigator) in Arm 3 vs Arm 1
  - Non-tBRCAm HRD-positive‡
  - ITT population

Key secondary endpoints

- PFS (RECIST per investigator) in Arm 2 vs Arm 1
  - ITT population
- OS
- Safety

DUO-O also included an independent, single-arm, open-label tBRCAm cohort – results are not presented

Treatment continued until disease progression, study treatment was complete or other discontinuation criteria were met

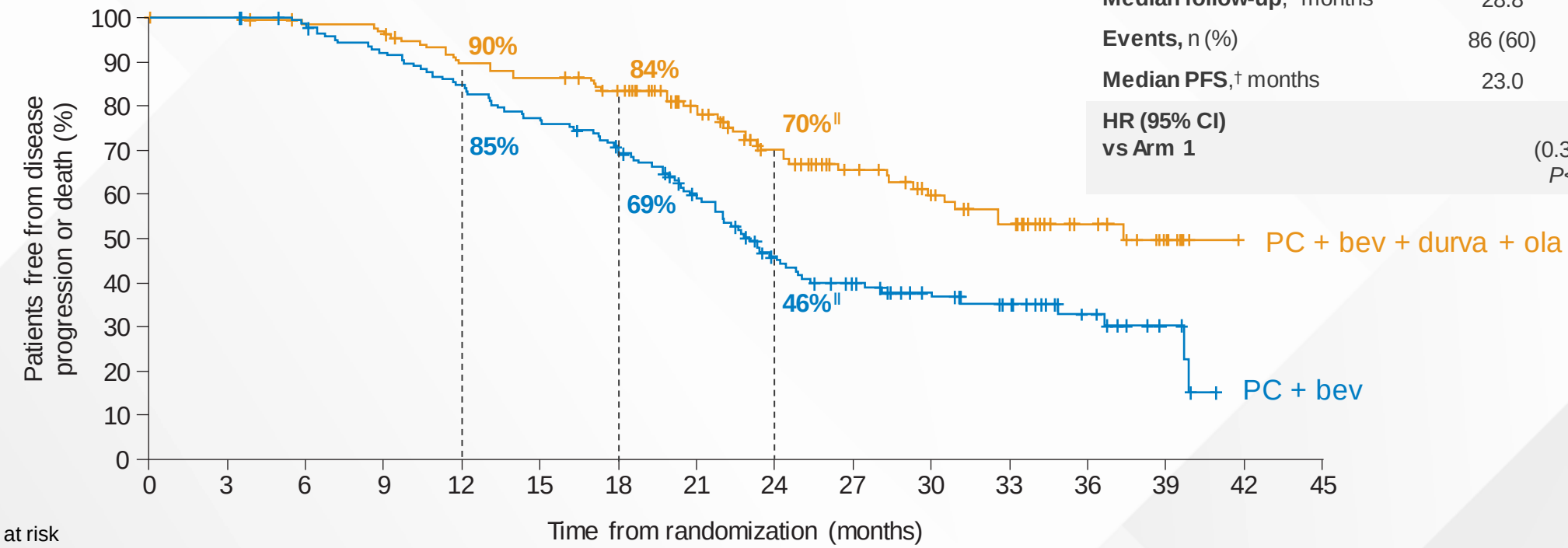
Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m^2 IV q3w and carboplatin at AUC5 or AUC6 IV q3w.
PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.

Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506.

AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; OC, ovarian cancer; ola, olaparib; OS, overall survival; PARP, poly(adenosine diphosphate ribose) polymerase; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

PFS: Non-tBRCAm HRD-Positive Population Arm 3 vs Arm 1

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Median follow-up,* months	28.8	25.6
Events, n (%)	86 (60)	49 (35)
Median PFS,† months	23.0	37.3‡
HR (95% CI) vs Arm 1	**0.49** (0.34–0.69)§ *P*<0.0001	



Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

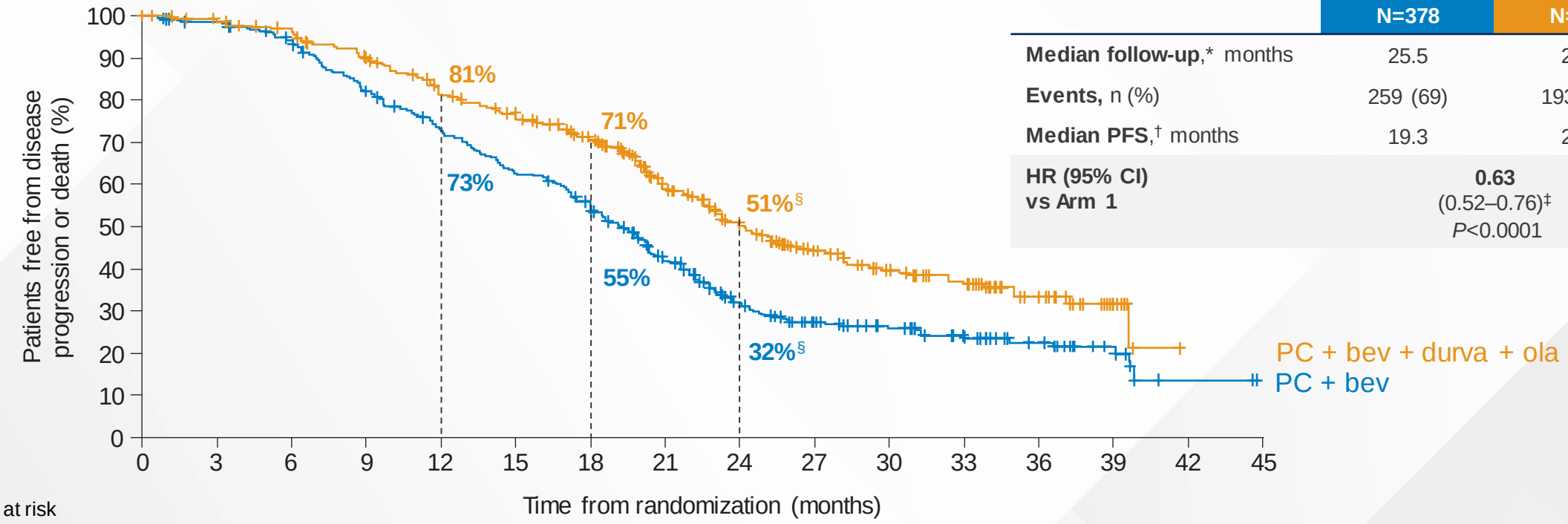
*In censored patients; †Medians and rates were estimated by KM method; ‡Median PFS in Arm 3 unstable; §HR and CI were estimated from a stratified Cox proportional hazards model. *P* value from a stratified log rank text. Model stratified by timing and outcome of cytoreductive surgery; ‖24-month PFS rates unstable.

Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506.

bev, bevacizumab; CI, confidence interval; durva, durvalumab; HR, hazard ratio; KM, Kaplan–Meier; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin.

PFS: ITT Population Arm 3 vs Arm 1

	Arm 1 PC + bev N=378	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.3
Events, n (%)	259 (69)	193 (51)
Median PFS,† months	19.3	24.2
HR (95% CI) vs Arm 1	**0.63** (0.52–0.76)‡ *P*<0.0001	



Patients at risk

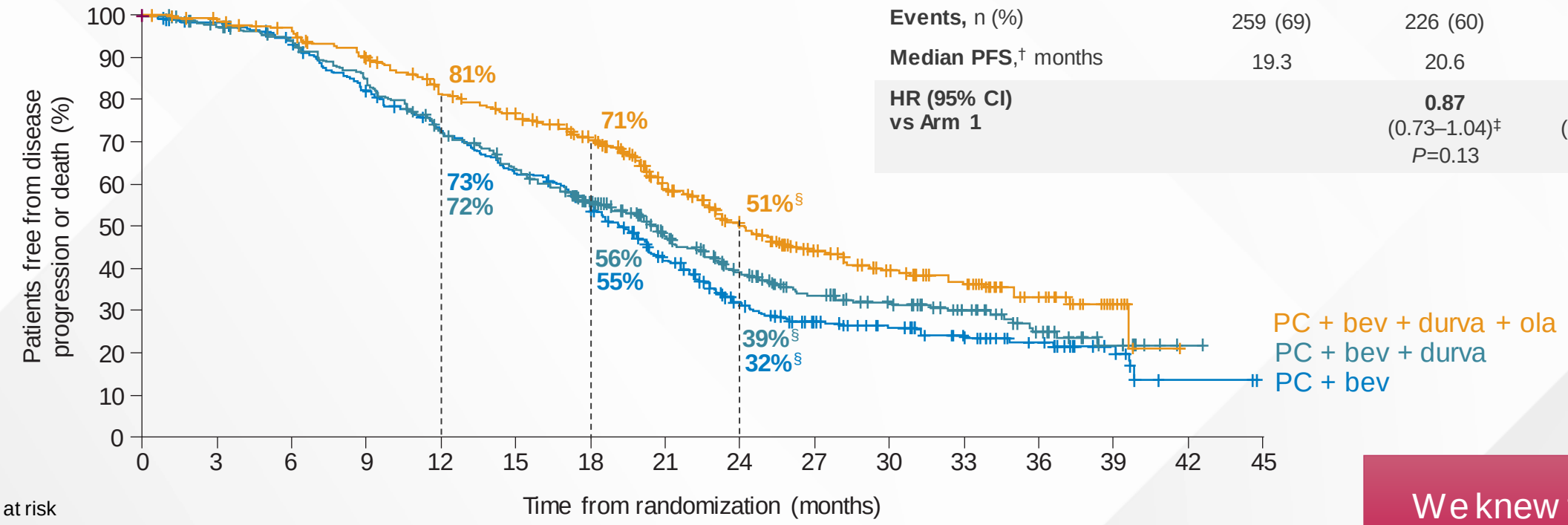
Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

*In censored patients; †Medians and rates were estimated by KM method; ‡HR and CI were estimated from a stratified Cox proportional hazards model. Model stratified by timing and outcome of cytoreductive surgery and geographical region. *P* value from a stratified log rank text; §24-month PFS rates unstable.

Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506.
bev, bevacizumab; CI, confidence interval; durva, durvalumab; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan–Meier; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin.

PFS: ITT Population

	Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.1	23.3
Events, n (%)	259 (69)	226 (60)	193 (51)
Median PFS,† months	19.3	20.6	24.2
HR (95% CI) vs Arm 1		**0.87** (0.73–1.04)‡ *P*=0.13	**0.63** (0.52–0.76)‡ *P*<0.0001



Patients at risk

Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 2	374	354	336	301	254	221	180	130	93	70	54	39	23	11	1	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

We knew this from IMagyn050

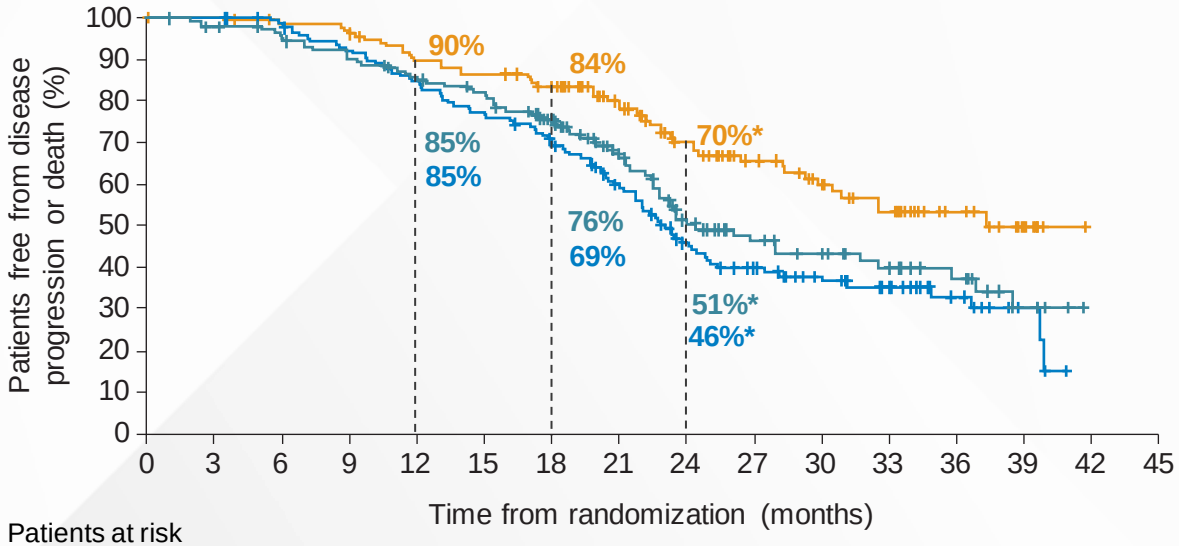
*In censored patients; †Medians and rates were estimated by KM method; ‡HR and CI were estimated from a stratified Cox proportional hazards model. Model stratified by timing and outcome of cytoreductive surgery and geographical region. *P* value from a stratified log rank text; §24-month PFS rates unstable.

Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506.

bev, bevacizumab; CI, confidence interval; durva, durvalumab; HR, hazard ratio; ITT, intent to treat; KM, Kaplan–Meier; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin.

Subgroup Analysis of PFS by HRD Status

Non-tBRCAm HRD-positive

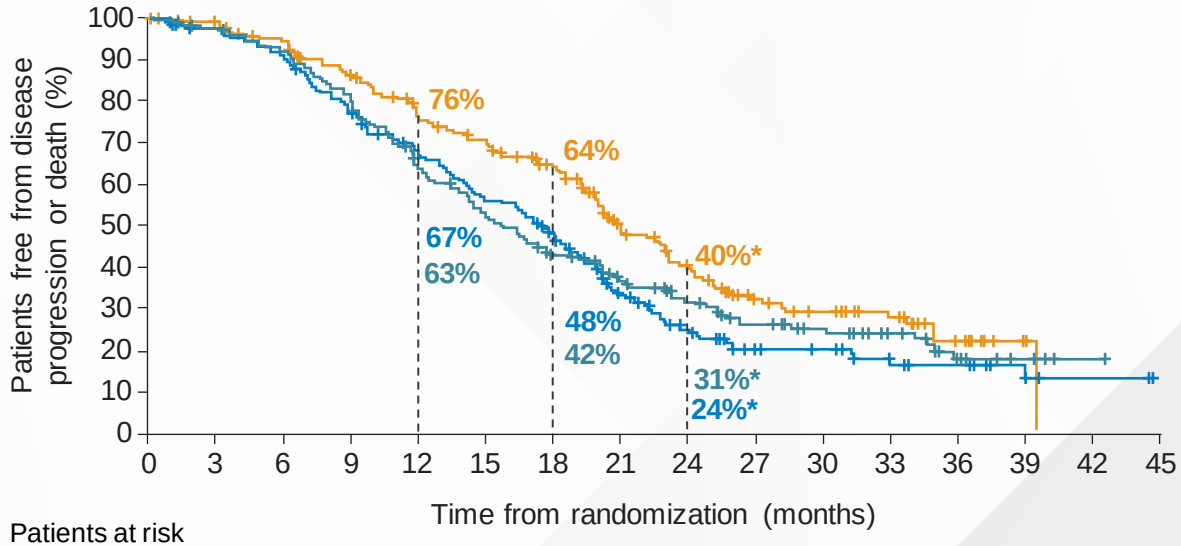


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

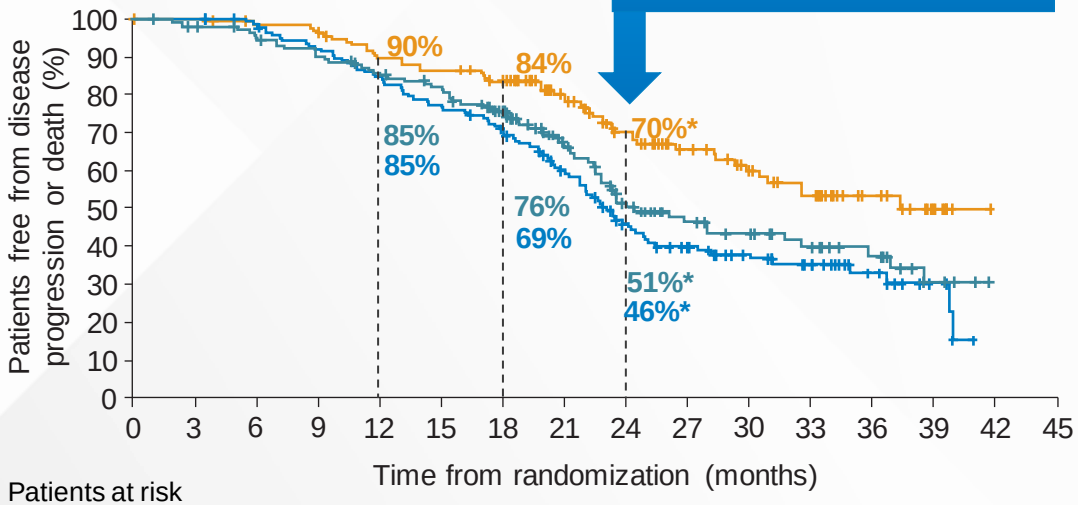
Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506.

bev, bevacizumab; durva, durvalumab; HRD, homologous recombination deficiency; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin.

DUO-O vs PAOLA-1: PFS in BRCAwt/HRD

Non-tBRCAm HRD-positive

You might be tempted to say that this



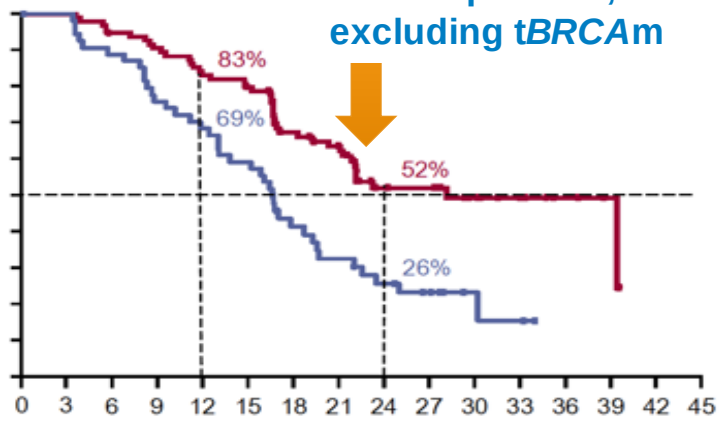
Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

Looks better than this

HRD-positive, excluding t*BRCA*m



Olaparib + Bevacizumab (N = 97)	Placebo + Bevacizumab (N = 55)
43 (44)	40 (73)
28.1*	16.6

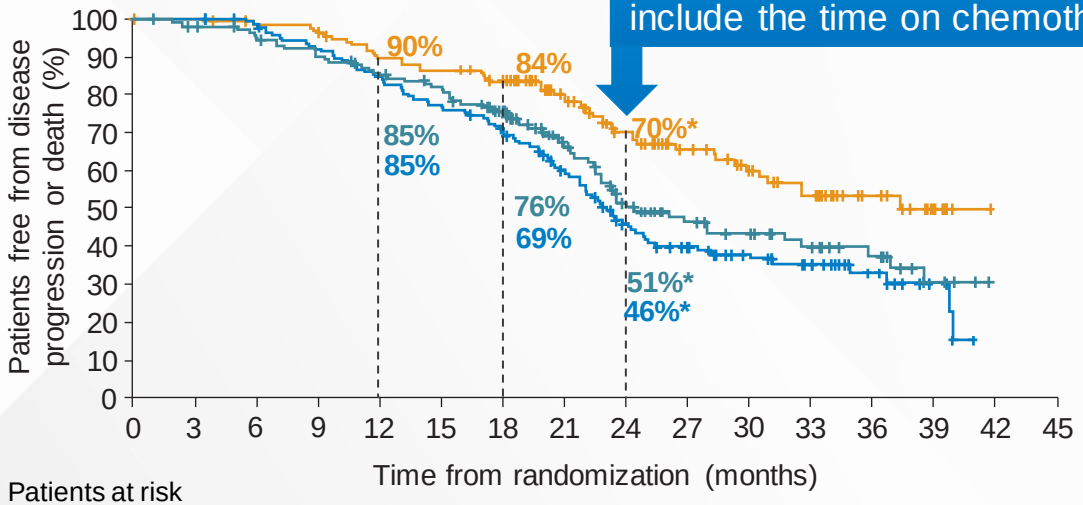
HR 0.43 (95% CI: 0.28, 0.66)

Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506. Ray-Coquard I, et al. ESMO Congress 2019. Abstract LBA2_PR.
bev, bevacizumab; BRCAwt, BRCA wild type; CI, confidence interval; durva, durvalumab; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent to treat; KM, Kaplan–Meier; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

DUO-O vs PAOLA-1: PFS in BRCAwt/HRD

Non-tBRCAm HRD-positive

But you would be forgetting that the KM curve for PAOLA does NOT include the time on chemotherapy



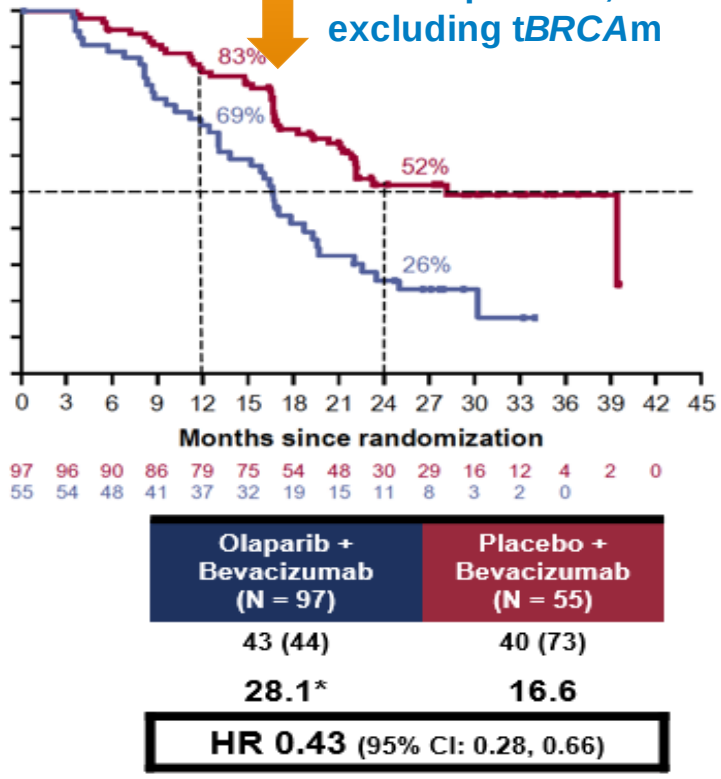
Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

So 24 months in DUO-O is around 18 months in PAOLA

HRD-positive, excluding t*BRCA*m

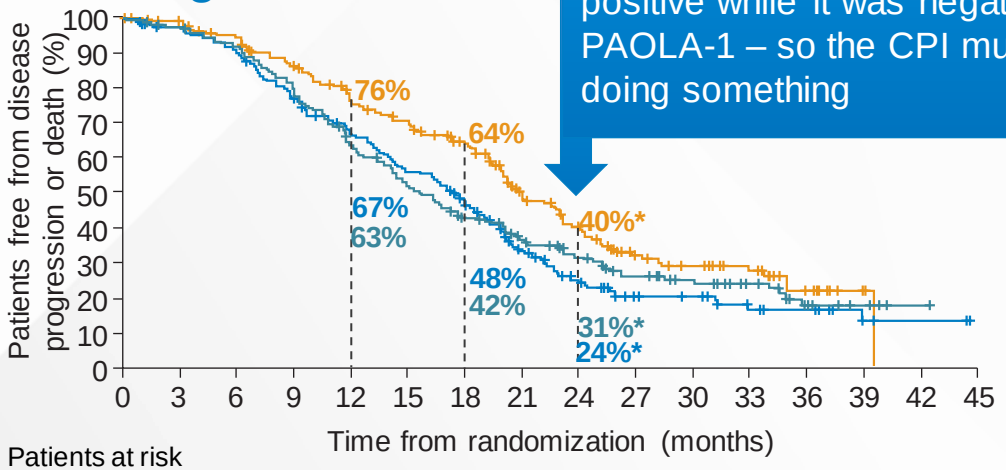


Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506. Ray-Coquard I, et al. ESMO Congress 2019. Abstract LBA2_PR.
bev, bevacizumab; BRCAwt, BRCA wild type; CI, confidence interval; durva, durvalumab; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent to treat; KM, Kaplan–Meier; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

DUO-O vs PAOLA-1: PFS in BRCAwt/HRD Test Negative

You might also be tempted to conclude that HRP in DUO-O is positive while it was negative in PAOLA-1 – so the CPI must be doing something

HRD-negative

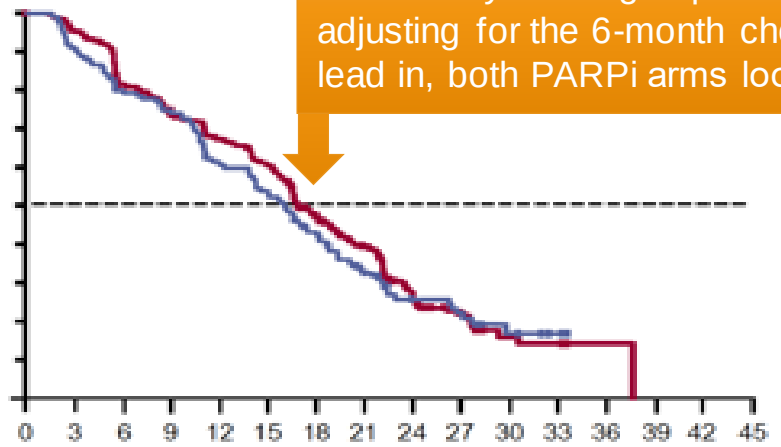


Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

This may be true or it may not be – this is a non-analytic subgroup. However, adjusting for the 6-month chemotherapy lead in, both PARPi arms look similar…



Olaparib + Bevacizumab (N = 282)	Placebo + Bevacizumab (N = 137)
193 (68)	102 (74)
16.9	16.0

HR 0.92 (95% CI: 0.72, 1.17)

Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506. Ray-Coquard I, et al. ESMO Congress 2019. Abstract LBA2_PR.
bev, bevacizumab; BRCAwt, BRCA wild type; CI, confidence interval; CPI, checkpoint inhibitors; durva, durvalumab; HR, hazard ratio; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; KM, Kaplan–Meier; ola, olaparib; PARPi, poly(ADP-ribose) polymerase inhibitor; PC, paclitaxel/carboplatin; PFS, progression-free survival.

Addition of CPI Will Have to Wait for One of These to Result…

Trial	Size	Anti-angiogenic	PARPi	CPI	Start	Estimated Primary Completion
FIRST[1] ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
DUO-O[2] ENGOT OV-46	~1254	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023
ATHENA[3] GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43[4] KEYLYNK-001	~1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	Aug 2025

AXIS Medical Education

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03602859. 2. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03737643. 3. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03522246. 4. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03740165.
CPI, checkpoint inhibitor.

PAOLA-1, PRIMA and ATHENA-MONO: Clinical Context of Trial Populations

PAOLA-1[1,2]
Olaparib + bevacizumab

Chemotherapy + bevacizumab → **Olaparib + bev**

Primary endpoint:

- Investigator-assessed PFS (ITT)

HRD status:

- Determined by Myriad MyChoice CDx (BRCA mutations and LOH, TAI and LST)

No selection for higher risk of relapse:

- PDS or IDS with residual / no residual disease

Weak selection for evaluable response to platinum:

- CR/PR (investigator)
- ~50% PDS of which 60% had no residual tumor
- Response partially based on bevacizumab
- Selection for response to bevacizumab in HRD-negative population

PRIMA[3,4]
Niraparib

- Chemotherapy → **Niraparib monotherapy**

Primary endpoint:

- PFS by BICR (HRD → ITT)

HRD status:

- Determined by Myriad MyChoice CDx (BRCA mutations and LOH, TAI and LST)

Selection for higher risk of relapse:

- Stage III PDS with residual disease
- Stage III IDS / Stage IV

Strong selection for evaluable response to platinum:

- CR/PR (investigator)
- All Stage III PDS patients had measurable disease to assess platinum response
- Normal or >90% ↓CA-125

ATHENA-MONO[5,a]
Rucaparib

Chemotherapy → **Rucaparib monotherapy**

Primary endpoint:

- Investigator-assessed PFS

HRD status:

- Determined by FoundationOne CDx (BRCA mutations and LOH)

No selection for higher risk of relapse:

- PDS or IDS with residual / no residual disease

Weak selection for evaluable response to platinum:

- CR/PR (investigator)
- ~49% of patients had PDS
- ~75% had no residual tumor

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

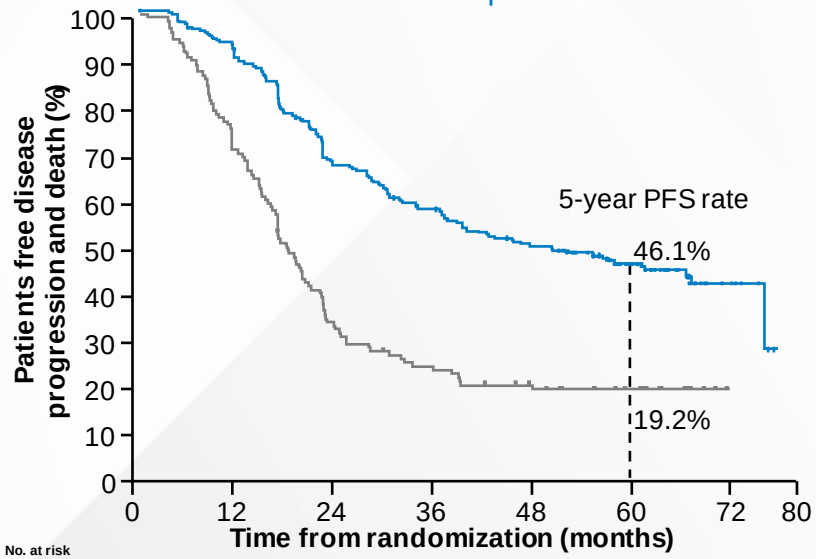
[a]Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.

Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. 2. González-Martín A, et al. ESMO Virtual Congress 2020. Abstract LBA33. 3. González-Martín A, et al. *N Engl J Med*. 2019;381:2391-2402. 4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016. 5. Monk JM, et al. *J Clin Oncol*. 2022;40(34):3952-3964.

bev, bevacizumab; BICR, blinded independent central review; BRCA, BRCA1 and/or BRCA2; CA-125, cancer antigen-125; CR, complete response; HRD, homologous recombination deficiency; IDS, interval debulking surgery; ITT, intention-to-treat; LOH, loss of heterozygosity; LST, large-scale state transition; NED, no evidence of disease; PDS, primary debulking surgery; PFS, progression-free survival; PR, partial response; TAI, telomeric allelic imbalance.

A Significant PFS Benefit From PARPi Was Observed in HRD-Positive Patient Populations

PAOLA-1[1]
PFS: HRD-positive



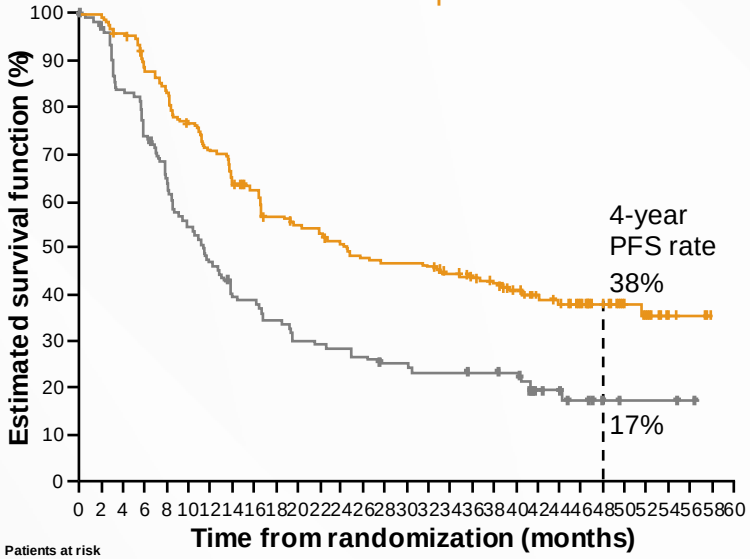
No. at risk

Olaparib + bevacizumab	255	252	242	236	223	214	194	183	165	162	147	143	138	127	123	119	117	112	103	79	63	40	31	8	5	3	0
Placebo + bevacizumab	132	129	118	103	91	79	62	52	41	37	34	30	29	25	24	24	21	20	19	15	13	8	6	2	0		

	Olaparib + bevacizumab	Placebo + bevacizumab
mPFS (months)	**46.8**	**17.6**

HR: 0.41 (95% CI: 0.32, 0.54)

PRIMA[2]
PFS: HRD-positive



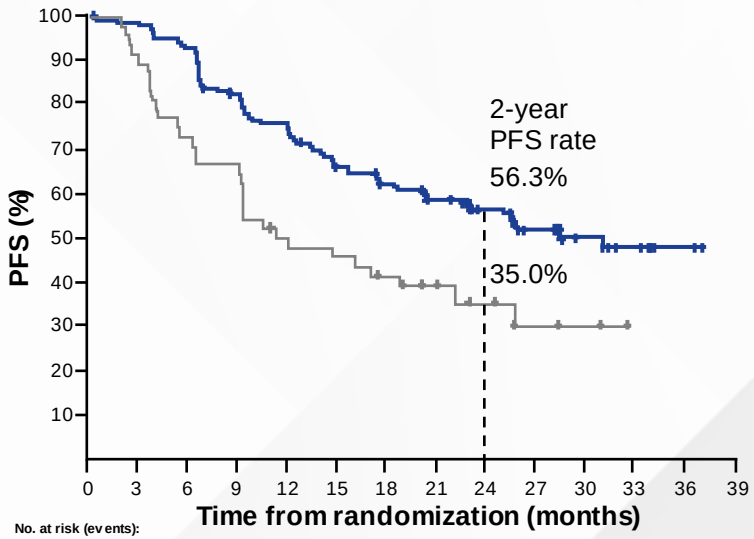
Patients at risk

Niraparib	247	236	222	200	190	174	159	144	138	125	119	116	110	103	101	101	99	92	87	82	71	48	45	38	21	17	15	4	2	1	0
Placebo	126	118	102	91	76	66	57	47	46	41	36	35	34	32	28	28	26	26	25	25	24	11	10	7	5	2	2	2	1	0	

	Niraparib	Placebo
mPFS (months)	**24.5**	**11.26**

HR: 0.52 (95% CI: 0.40, 0.68)

ATHENA-MONO[3,a]
PFS: HRD-positive



No. at risk (events):

Rucaparib	185 (0)	175 (3)	165 (12)	143 (31)	127 (46)	110 (60)	100 (66)	82 (71)	59 (74)	36 (78)	22 (79)	12 (80)	3 (80)	0 (80)
Placebo	49 (0)	43 (5)	35 (13)	32 (16)	22 (25)	21 (26)	18 (28)	11 (29)	8 (30)	4 (31)	2 (31)	0 (31)		

	Rucaparib	Placebo
mPFS (months)	**28.7**	**11.3**

HR: 0.47 (95% CI: 0.31, 0.72)

Please note that head-to-head studies were not conducted between these products. Data represent active comparators (colours) vs placebo (grey). In PAOLA-1, patients in the placebo arm also received bevacizumab. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

[a]Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.

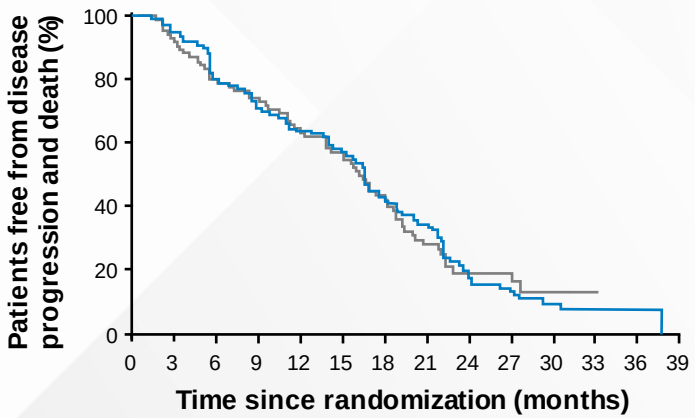
1. Ray-Coquard I, et al. ESMO Annual Meeting 2022. Abstract #LBA29. 2. Gonzales-Martin A, et al. ESMO Annual Meeting 2022. Abstract #530P. 3. Monk JM, et al. *J Clin Oncol.* 2022;40(34):3952-3964.

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; mPFS, median progression-free survival; PARPi, poly(ADP-ribose) polymerase inhibitor.

What About Patients With HRD-Negative Tumors? PFS Analyses from PAOLA-1, PRIMA, and ATHENA-MONO

PAOLA-1[1]

PFS: HRD-negative

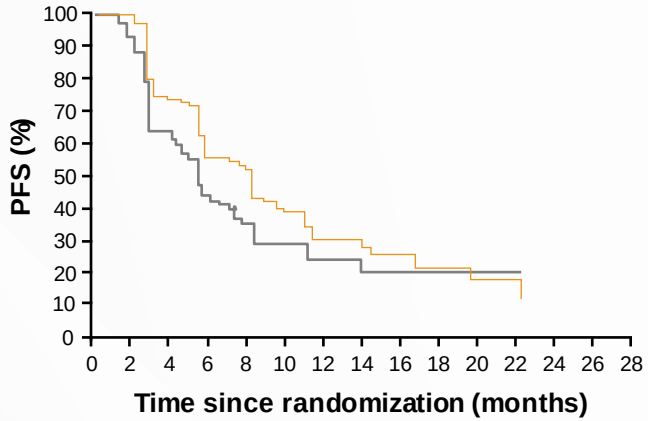


	Olaparib + bevacizumab	Placebo + bevacizumab
mPFS (months)	16.6	16.2
HR (95% CI)	1.00 (0.75, 1.35)	

There was no additional benefit from adding PARP inhibitors on top of bevacizumab in HRD-negative patients

PRIMA[2,3]

PFS: HRD-negative

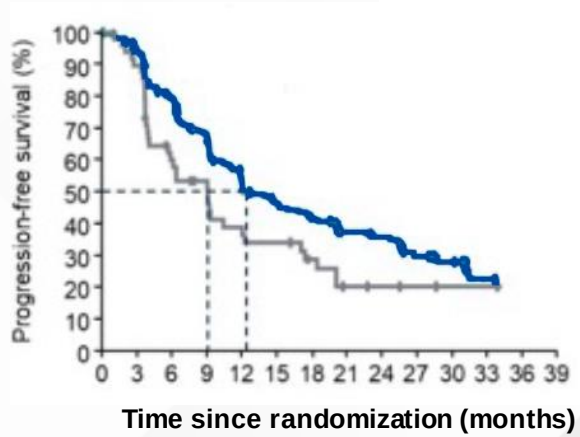


	Niraparib	Placebo
mPFS (months)	8.1	5.4
HR (95% CI)	0.68 (0.49, 0.94)	

Niraparib showed PFS benefit in the HRD-negative subgroup (2.7 months)

ATHENA-MONO[4,a]

PFS: BRCA^{wt}/LOH^{low}



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

Rucaparib PFS in exploratory subgroups BRCA^{wt}/LOH^{low}

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

[a]Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.

1. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. 2. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 3. Monk BJ, et al. SGO 2020. Abstract 31. 4. Monk BJ, et al. ASCO Annual Meeting 2022. Abstract LBA5500.

BRCA, *BRCA1* and/or *BRCA2*; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; (m)PFS, (median) progression-free survival; PARP, poly(adenosine diphosphate ribose) polymerase; wt, wild-type.

PARP Inhibitors as Maintenance Therapy and Treatment for Relapsed/Recurrent Advanced Ovarian Cancer

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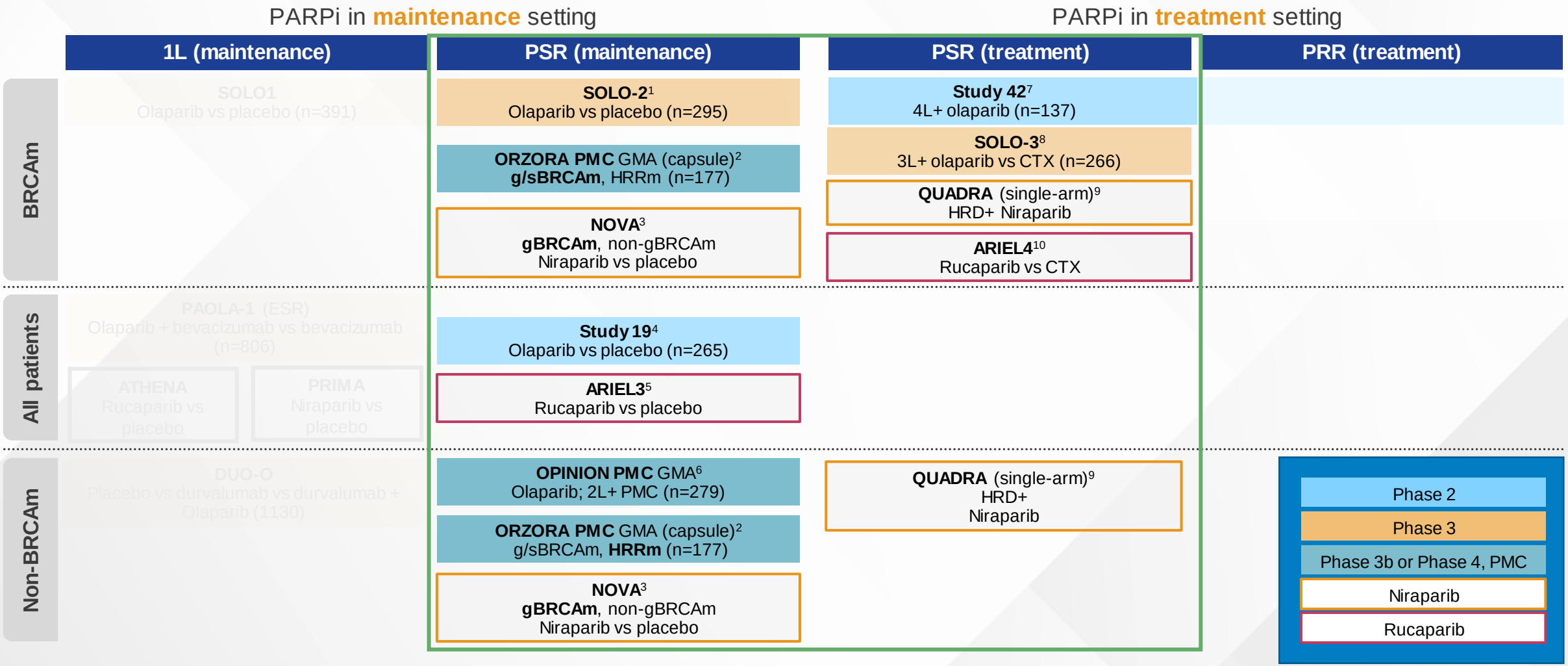
Phase II/III Studies of PARP Inhibitors in Ovarian Cancer Management



1. Poveda A, et al. *Lancet Oncol*. 2021;22(5):620-631. 2. Pignata S, et al. *Gynecologic Oncol*. 2023;172:121-129. 3. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-2164. 4. Ledermann JA, et al. *Ther Adv Med Oncol*. 2019;11:1758835919849753. 5. Coleman RL, et al. *The Lancet* 2017;390:1949-1961. 6. Poveda A, et al. *Gynecol Oncol*. 2022;164(3):498.504. 7. Domchek SM, et al. *Gynecol Oncol*. 2016;140(2):199.203. 8. Penson RT, et al. *J Clin Oncol*. 2020;38(11):1164-1174. 9. Moore K, et al. *Lancet Oncol*. 2019;20(5):636-648. 10. Kristeleit R, et al. *Lancet Oncol* 2022;23(4):465-478. 11. Cadoo K, et al. *Gynecol Oncol*. 2022;166(3):425-431.

1/2/3/4L, first/second/third/fourth line; CTX, chemotherapy; GMA, Global Medical Affairs; g/sBRCAm, germline/somatic *BRCA1* and/or *BRCA2* mutation; HRD, homologous recombination deficiency; HRRm, homologous recombination repair gene mutation; OC, ovarian cancer; PARPi, poly(ADP-ribose) polymerase inhibitor; PMC, post-marketing commitment; PRR, platinum-resistant relapse(d); PSR, platinum-sensitive relapse(d).

PARPi Maintenance Treatment Clinical Trials in Relapsed OC

	Phase	PARPi	Comparator	OS (HR)			PFS (HR)		
				ITT	BRCAm	Non-BRCAm	ITT	BRCAm	Non-BRCAm
Study 19[1–3]	2	Olaparib	Placebo	0.73	0.62	0.84	0.35	0.18	0.54
SOLO-2[4,5]	3	Olaparib	Placebo	-	0.74	-	0.30	0.33	-
NOVA[6,7]	3	Niraparib	Placebo	-	0.85	**1.06**	-	0.27	0.45
ARIEL3[8,9]	3	Rucaparib	Placebo	0.995	0.83	**1.280** (LOH-high) **1.153** (LOH-low)	0.36	0.23	0.44 (LOH-high) 0.58 (LOH-low)

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

1. Ledermann JA, et al. *N Engl J Med.* 2012;366:1382-1392. 2. Ledermann JA, et al. *Lancet Oncol.* 2014;15(8):852-861. 3. Friedlander M, et al. *Br J Cancer.* 2018;119:1075-1085. 4. Poveda A, et al. *Lancet Oncol.* 2021;22(5):620-631. 5. Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-1284. 6. Matulonis U, et al. SGO Annual Meeting 2023. Abstract LBA 6. 7. Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-2164. 8. Coleman RL, et al. IGCS Annual Global Meeting 2022. Abstract 557. 9. Coleman R, et al. *Lancet.* 2017;390:1949-1961.

HR, hazard ratio; g/sBRCAm, germline/somatic *BRCA1* and/or *BRCA2* mutation; LOH, hoss of heterozygosity; ITT, intention to treat; OC, ovarian cancer; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

PARPi Treatment Clinical Trials in Later-Line Relapsed OC

	Phase	PARPi	Comparator	OS (HR)			PFS
				BRCAm	HRD-positive	HRD-negative	BRCAm
SOLO-3[1,2]	3	Olaparib	Chemotherapy	(≥2 prior lines of chemo) 1.07 (≥3 prior lines of chemo) 1.33	-	-	0.62
ARIEL4[3,4]	3	Rucaparib	Chemotherapy	1.31[a]	-	-	0.67[a]
QUADRA[5]	2 (**single-arm**)	Niraparib	-	mOS: 26.0 months	mOS: 19.0 months	mOS: 15.5 months	-

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

[a]Intention-to-treat population.

1. AstraZeneca. https://www.lynparzahcp.com/content/dam/physician-services/us/590-lynparza-hcp-branded/hcp-global/pdf/solo3-dhcp-final-signed.pdf. 2. Penson RT, et al. *J Clin Oncol.* 2020;38:1164-1174. 3. Clovis Oncology. https://clovisoncology.com/pdfs/US_DHCPL_final_signed.pdf. 4. Kristeleit R, et al. *Lancet Oncol.* 2022;23(4):465-478. 5. Moore KN, et al. *Lancet Oncol.* 2019;20(5):636-648.

BRCAm, *BRCA1* and/or *BRCA2* mutation; HR, hazard ratio; OC, ovarian cancer; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

OS Results in Non-BRCAm Patients From ARIEL3 and NOVA Has Led to Restriction of the PSR Label in the US

Olaparib FDA-approved indication[1]

For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy

Rucaparib FDA-approved indication[2]

For the maintenance treatment of adult patients with a **deleterious BRCA mutation (germline and/or somatic)**-associated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy

Niraparib FDA-approved indication[3]

For the maintenance treatment of adult patients with **gBRCAm** recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy

EMA label for olaparib, rucaparib, and niraparib remain unchanged in this setting

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1. LYNPARZA (olaparib). Prescribing Information. AstraZeneca; 2023. 2. RUBRACA (rucaparib). Prescribing information. Clovis Oncology; 2022. 3. GSK. https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%20(niraparib)%20Dear%20HCP%20Letter%20November%202022.pdf.

EMA, European Medicines Agency; FDA, food and drug administration; gBRCAm, germline *BRCA*1 and/or *BRCA*2 mutation; OC, ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PSR, platinum-sensitive relapsed.

Key Takeaways and Considerations

- Most patients with advanced ovarian cancer relapse following first-line multimodality therapy
- Multiple lines of chemotherapy is associated with cumulative toxicity while remission periods decrease
- First-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure
- Significant progress has been made in the management of ovarian cancer over the past decade
  - Bevacizumab
  - PARP inhibitors for BRCA-mutated ovarian cancer
  - PARP inhibitors beyond BRCA mutation
- PARP inhibitors as first-line maintenance:
  - SOLO-1: olaparib (BRCAm)
  - PAOLA-1: olaparib + bevacizumab (HRD+)
  - PRIMA: niraparib (all patients)
  - ATHENA-MONO: rucaparib (investigational)
- Earlier introduction of PARP inhibitors may benefit significant numbers of patients
- Benefits of delaying chemotherapy in some patients and use of PARP inhibitors in maintenance regimens
- Considerations when selecting therapy:
  - Patient response to platinum therapy
  - BRCA and HRD testing and biomarker status
  - Route of administration
  - Guideline recommendations
  - Shared decision-making
- Importance of consultation and referral to gynecologic oncologists

HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.