PARP Inhibitors in Frontline Maintenance: The Evolving Treatment Paradigm

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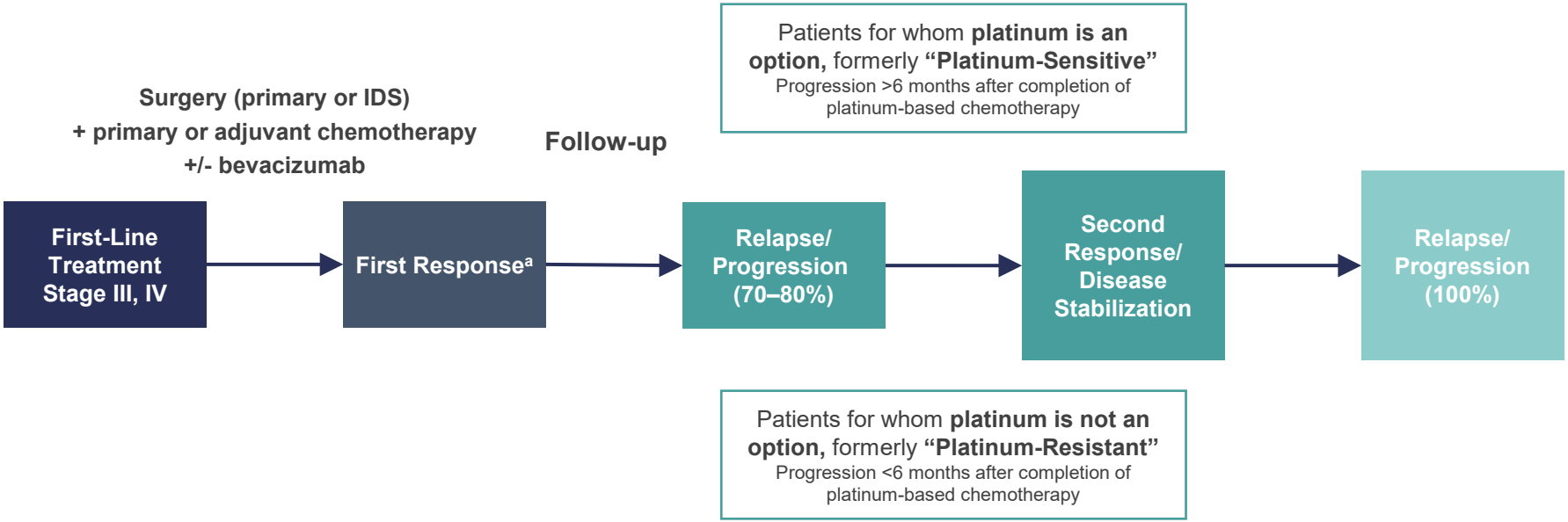
The typical course of advanced ovarian cancer[1–5]

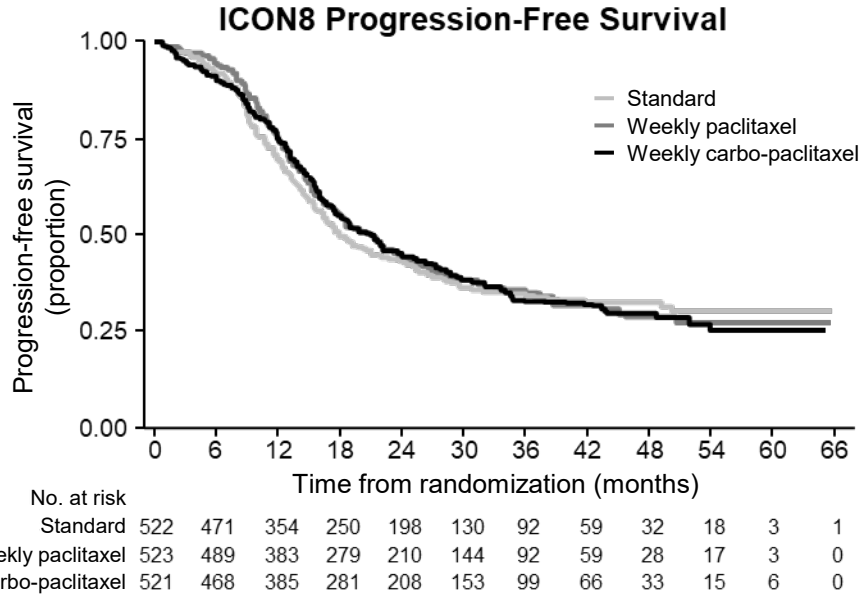


[a] Around 5% of patients are primary treatment–refractory, meaning that disease progressed during therapy or within 4 weeks after the last dose.

IDS, interval debulking surgery.

1. Ledermann JA et al. *Ann Oncol*. 2013;24(suppl 6):vi24–vi32. 2. Giornelli GH. *Springerplus*. 2016;5(1):1197. 3. Pignata S et al. *Ann Oncol*. 2017;28(suppl 8):viii51–viii56. 4. du Bois A et al. *Cancer*. 2009;115(6):1234–1244. 5. Wilson MK et al. *Ann Oncol*. 2017;28(4):727–732.

What can we expect with platinum-based chemotherapy alone?



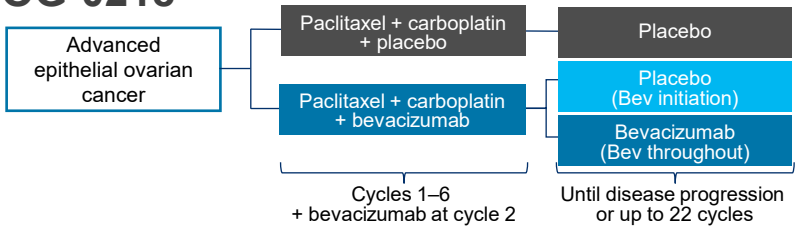
	Standard (n=522)	Weekly paclitaxel (n=523)	Weekly carbo-paclitaxel (n=521)
Progressions, n (%)	330 (63%)	335 (64%)	338 (65%)
Median PFS, months	17.9	20.6	21.1
Log rank (vs standard)		*P*=0.45	*P*=0.56
HR vs standard (97.5% CI)		**0.92 (0.77–1.09)**	**0.94 (0.79–1.12)**
Restricted means, months	24.4	24.9	25.3

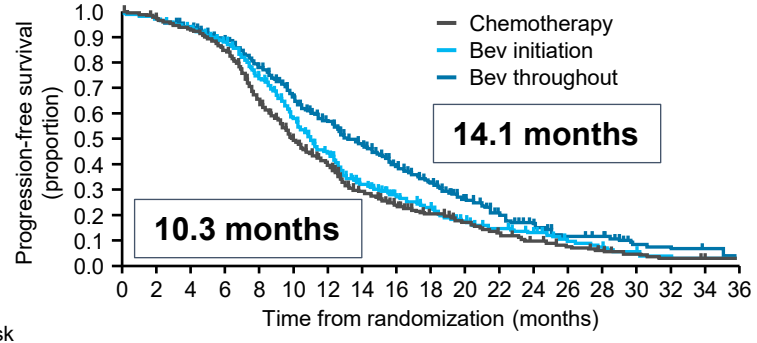
Weekly dose-dense chemotherapy can be delivered successfully as first-line epithelial ovarian cancer treatment without a substantial toxicity increase; it does not significantly improve PFS compared with standard 3-weekly chemotherapy

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Clamp AR et al. ESMO Congress 2017; Abstract 4427.

Platinum-based chemotherapy + bevacizumab and bevacizumab maintenance improved PFS

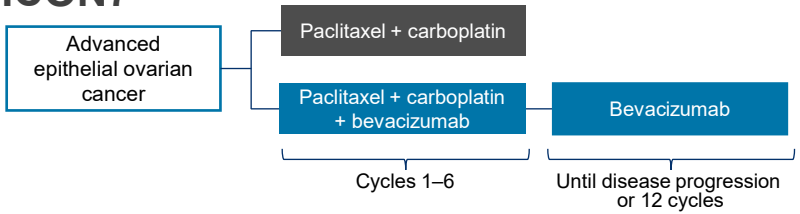
GOG-0218[1]

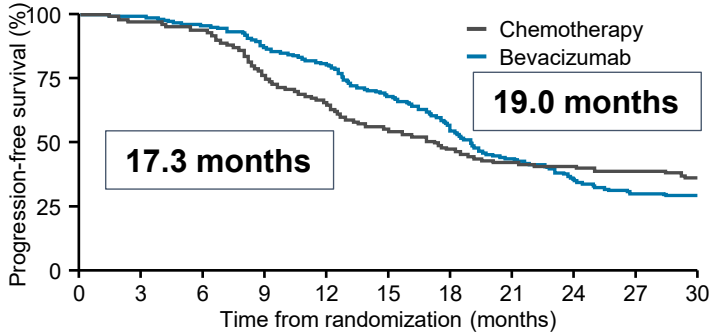




No. at risk				
Chemotherapy	625	199	33	8
Bev initiation	625	219	29	6
Bev throughout	623	254	38	8

ICON7[2]



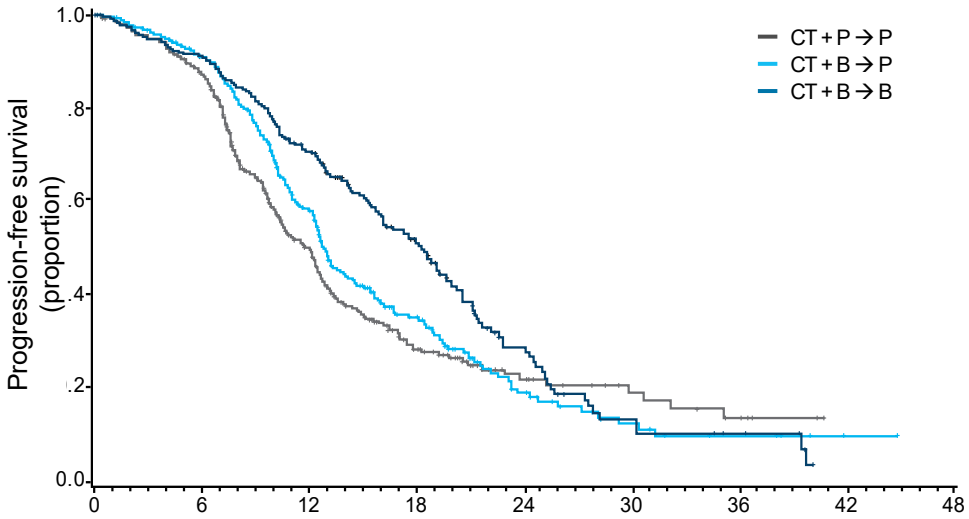


No. at risk						
Chemotherapy	764	693	464	216	91	25
Bevacizumab	764	715	585	263	73	19

Bev, bevacizumab; PFS, progression-free survival.

1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473–2483. 2. Perren TJ et al. *N Engl J Med*. 2011;365(26):2484–2496.

GOG-0218: FDA-approved indication

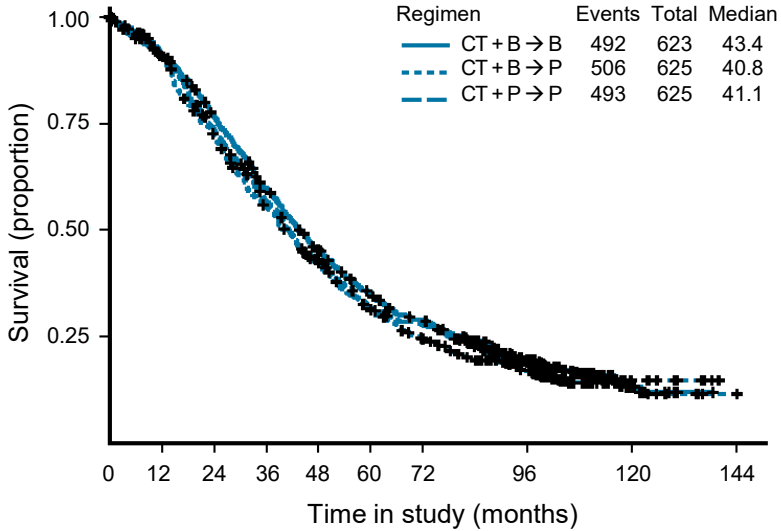


Efficacy parameter	Avastin with carboplatin and paclitaxel followed by Avastin alone (n=623)	Avastin with carboplatin and paclitaxel (n=625)	Carboplatin and paclitaxel (n=625)
Progression-free survival per investigator			
Median, months	**18.2**	**12.8**	**12.0**
Hazard ratio (95% CI)[a]	0.62 (0.52, 0.75)	0.83 (0.70, 0.98)	
P value[b]	<0.0001	NS	
Overall survival[c]			
Median, months	43.8	38.8	40.6
Hazard ratio (95% CI)[a]	0.89 (0.76, 1.05)	1.06 (0.90, 1.24)	

[a] Relative to the control arm; stratified hazard ratio. [b] Two-sided *P* value based on re-randomization test. [c] Final overall survival analysis.
B, bevacizumab; CI, confidence interval; CT, chemotherapy; NS, not significant; P, placebo.
Bevacizumab package insert. Genentech, Inc; January 2021.

GOG-0218: final overall survival

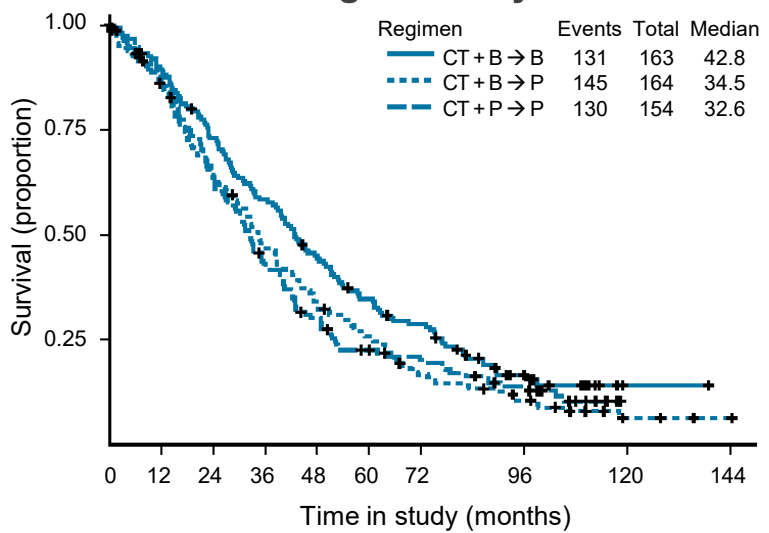
Final protocol-specified OS



No. at risk

CT + B → B	623	561	464	358	267	201	161	85	11	0
CT + B → P	625	558	443	334	252	185	136	74	11	1
CT + P → P	625	558	448	340	252	183	158	90	9	0

Exploratory subset Stage IV analyses



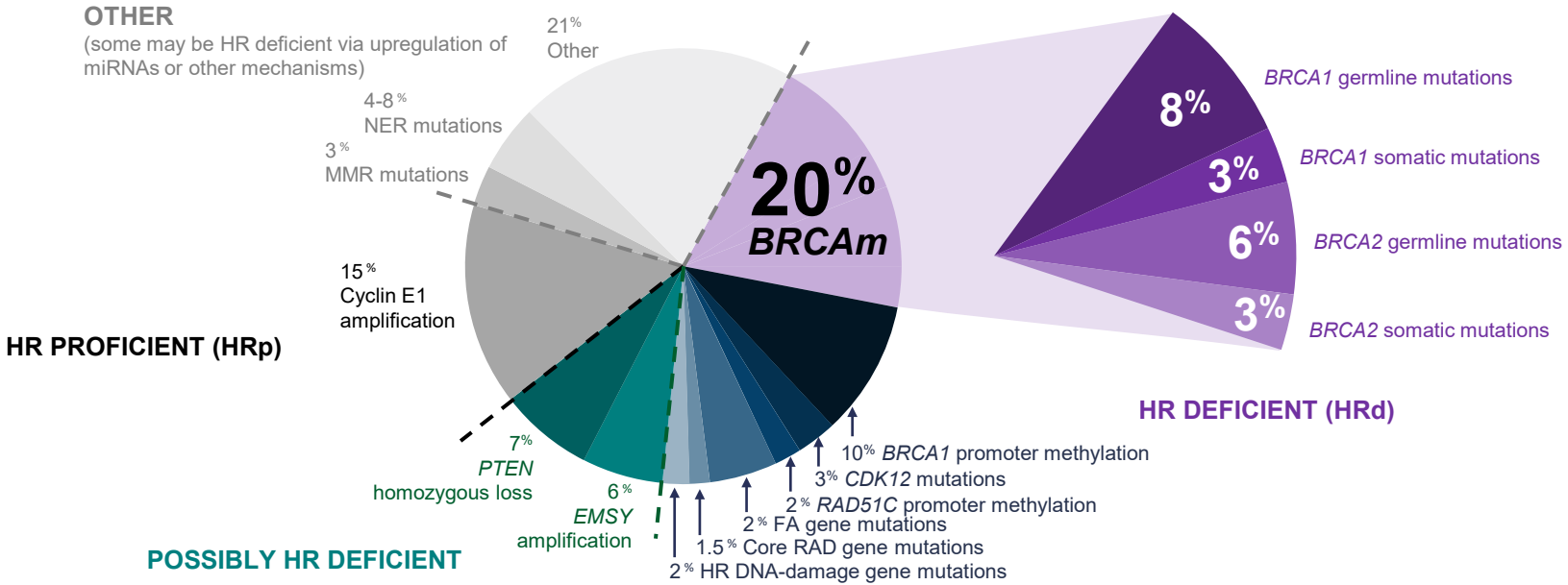
No. at risk

CT + B → B	163	142	115	92	70	53	43	17	1	0
CT + B → P	164	139	104	74	51	40	25	14	3	1
CT + P → P	154	130	96	64	44	31	26	14	0	

B, bevacizumab; CT, chemotherapy; OS, overall survival; P, placebo.

Tewari KS et al. *J Clin Oncol.* 2019;37(26):2317–2328.

An estimated 50% of epithelial ovarian cancers are HRd, and approximately 20% harbor *BRCA1/2* mutations

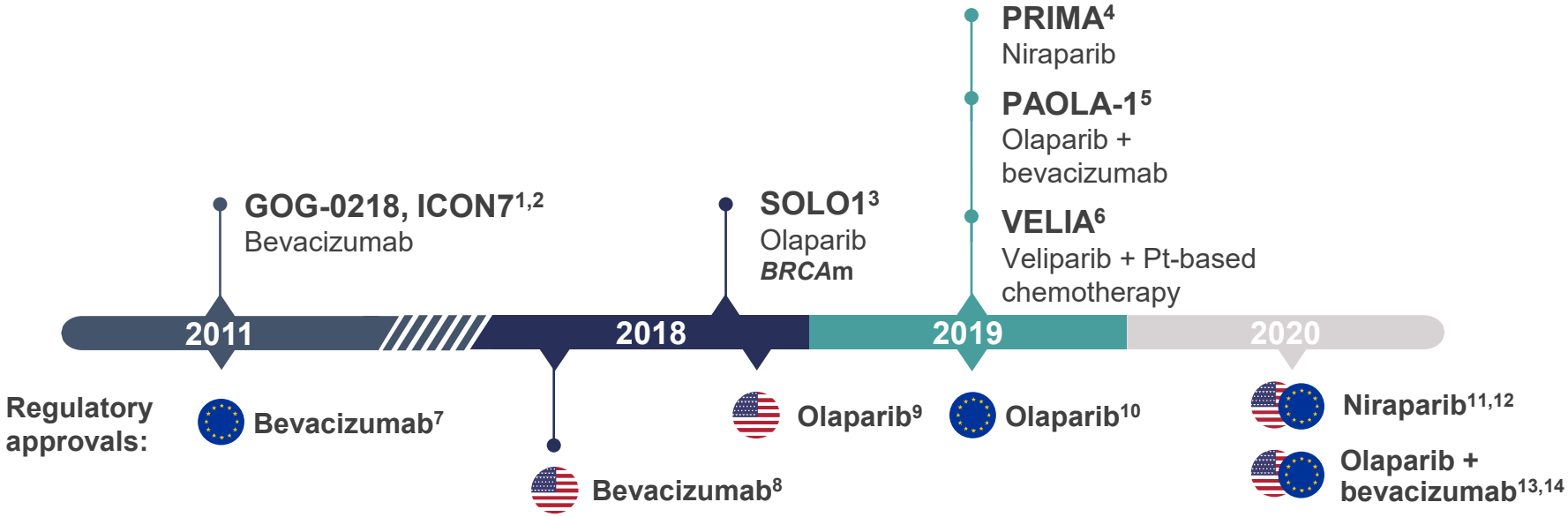


In women with HGSOC, an estimated 1 in 5 will have a *BRCA* mutation and an estimated 1 in 2 will be classified as having HRd disease

BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; *CDK12*, cyclin-dependent kinase 12; *EMSY*, EMSY transcriptional repressor, BRCA2 interacting; FA, Fanconi anemia; HGSOC, high-grade serous ovarian cancer; HR, homologous recombination; HRd, HR deficient; HRp, HR proficient; miRNA, microRNA; MMR, mismatch repair; NER, nucleotide excision repair; *PTEN*, phosphatase and tensin homolog; *RAD51C*, RAD51 paralog C.

Konstantinopoulos PA et al. *Cancer Discov*. 2015;5(11):1137–1154.

Pivotal trials and regulatory milestones in 1L maintenance therapy for advanced ovarian cancer



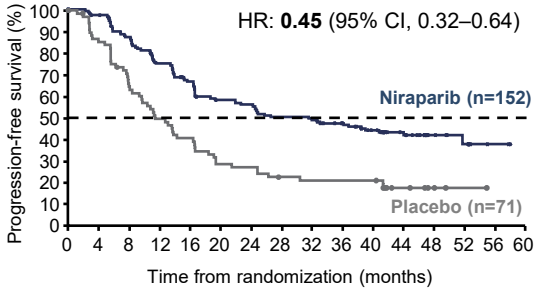
Dates shown indicate the year of the publication of the pivotal studies and regulatory approvals for these compounds.

1L, first line; *BRCA*, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; GOG, Gynecologic Oncology Group; Pt, platinum.

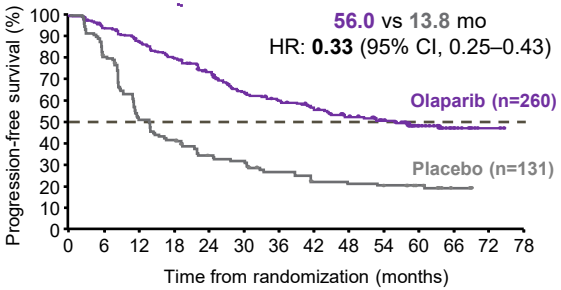
1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473–2483. 2. Perren TJ et al. *N Engl J Med*. 2011;365(26):2484–2496. 3. Moore K et al. *N Engl J Med*. 2018;379(26):2495–2505. 4. González-Martín A et al. *N Engl J Med*. 2019;381(25):2391–2402. 5. Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416–2428. 6. Coleman RL et al. *N Engl J Med*. 2019;381(25):2403–2415. 7. European Medicines Agency. Published Sep 22, 2011. Accessed Sep 23, 2022. 8. F. Hoffmann-La Roche Ltd. Published Jun 12, 2018. Accessed Sep 25, 2022. 9. US Food and Drug Administration. Published Dec 26, 2018. Accessed Sep 27, 2022. 10. European Medicines Agency. Published Apr 26, 2019. Accessed Sep 25, 2022. 11. GlaxoSmithKline. Published Apr 29, 2020. Accessed Sep 25, 2022. 12. GlaxoSmithKline. Published Oct 29, 2020. Accessed Sep 25, 2022. 13. US Food and Drug Administration. Published May 11, 2020. Accessed Sep 27, 2022. 14. European Medicines Agency. Published Sep 17, 2020. Accessed Sep 25, 2022.

PARP inhibitors are changing the course of disease for patients with *BRCA*m/HRd ovarian cancer

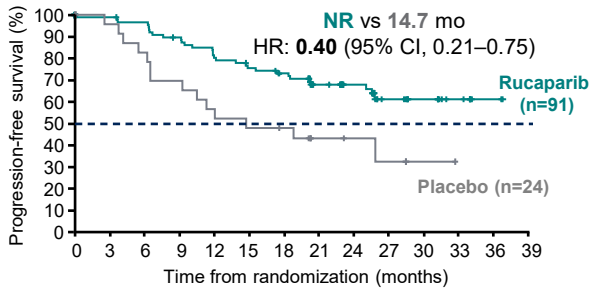
PRIMA: *BRCA*m HRd [1]



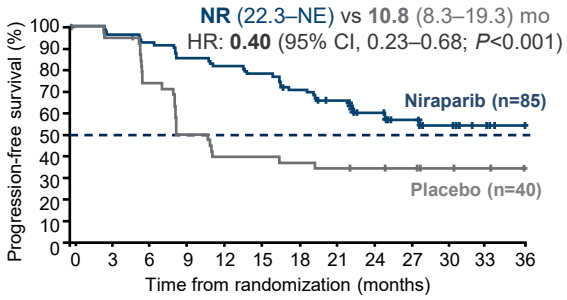
SOLO1: *BRCA*m[3]



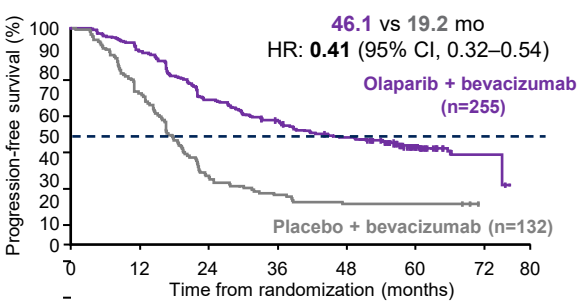
ATHENA-MONO: *BRCA*m HRd [5]



PRIME: *BRCA*m[2]



PAOLA-1: *BRCA*m HRd [4]

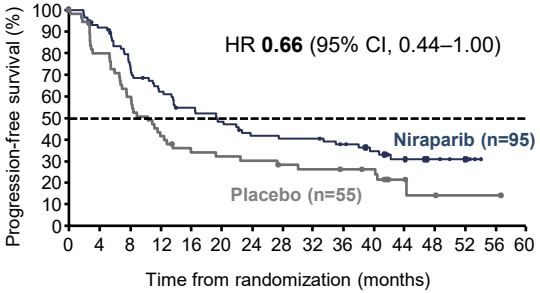


BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; HR, hazard ratio; HRd, homologous recombination deficient; mo, months; NE, not estimable; NR, not reached; PARP, poly (ADP-ribose) polymerase.

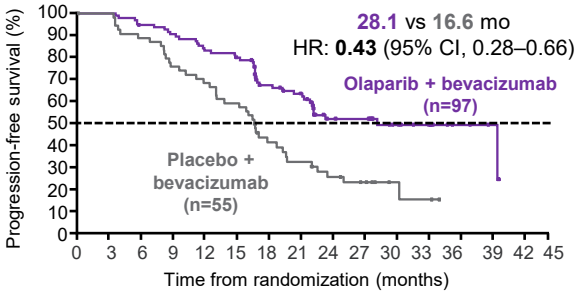
1. González-Martín A et al. ESMO Congress 2022; Abstract 530P. 2. Li N et al. SGO Annual Meeting on Women's Cancer 2022; Abstract LBA 5. 3. Bradley W et al. SGO Virtual Annual Meeting on Women's Cancer 2021; Abstract 10520. 4. Ray-Coquard I et al. ESMO Congress 2022; Abstract LBA29. 5. Monk BJ et al. ASCO Annual Meeting 2022; Abstract LBA5500.

PFS benefit of PARPi maintenance still present but decreased in *BRCA*wt/HRd cohorts compared to *BRCA*m cohorts

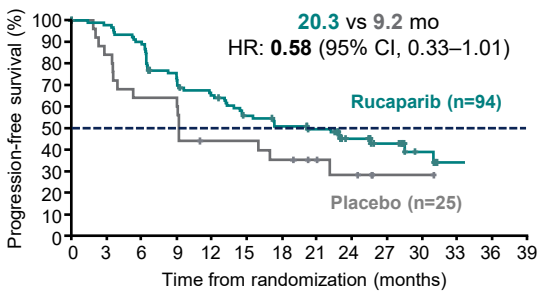
PRIMA: *BRCA*wt HRd [1]



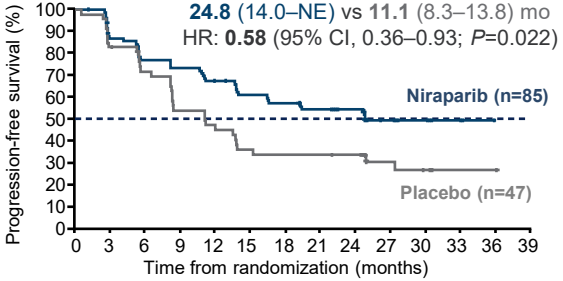
PAOLA-1: non-*BRCA*m HRd [3]



ATHENA-MONO: *BRCA*wt HRd [4]



PRIME: non-*BRCA*m HRd [2]

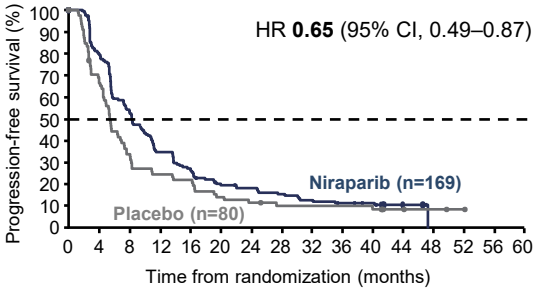


BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild type; CI, confidence interval; HR, hazard ratio; HRd, homologous recombination deficient; mo, months; NE, not estimable; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

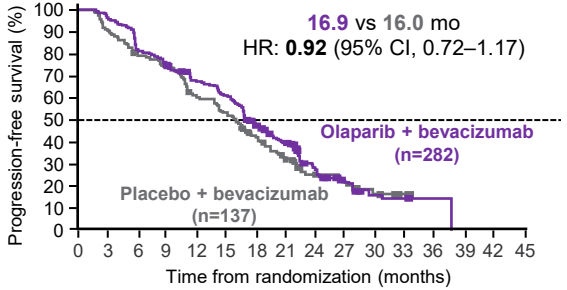
1 González-Martín A et al. ESMO Congress 2022; Abstract 530P. 2. Li N et al. SGO Annual Meeting on Women's Cancer 2022; Abstract LBA 5. 3. Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416–2428. 4. Monk BJ et al. ASCO Annual Meeting 2022; Abstract LBA5500.

PARPi maintenance observed to be less effective in HRp disease, with mixed PFS results across trials

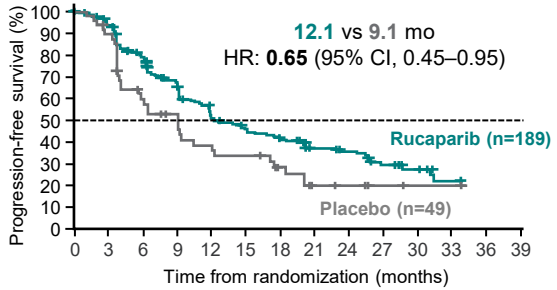
PRIMA: HRp[1]



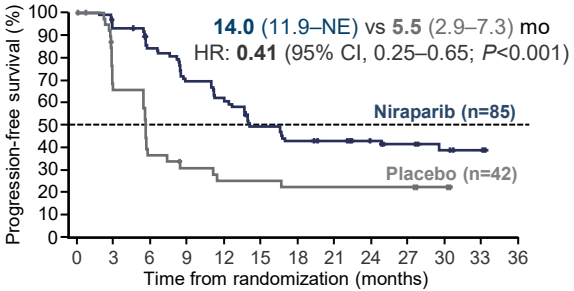
PAOLA-1: HRD-negative/unknown[3]



ATHENA-MONO: HRD-negative[4]



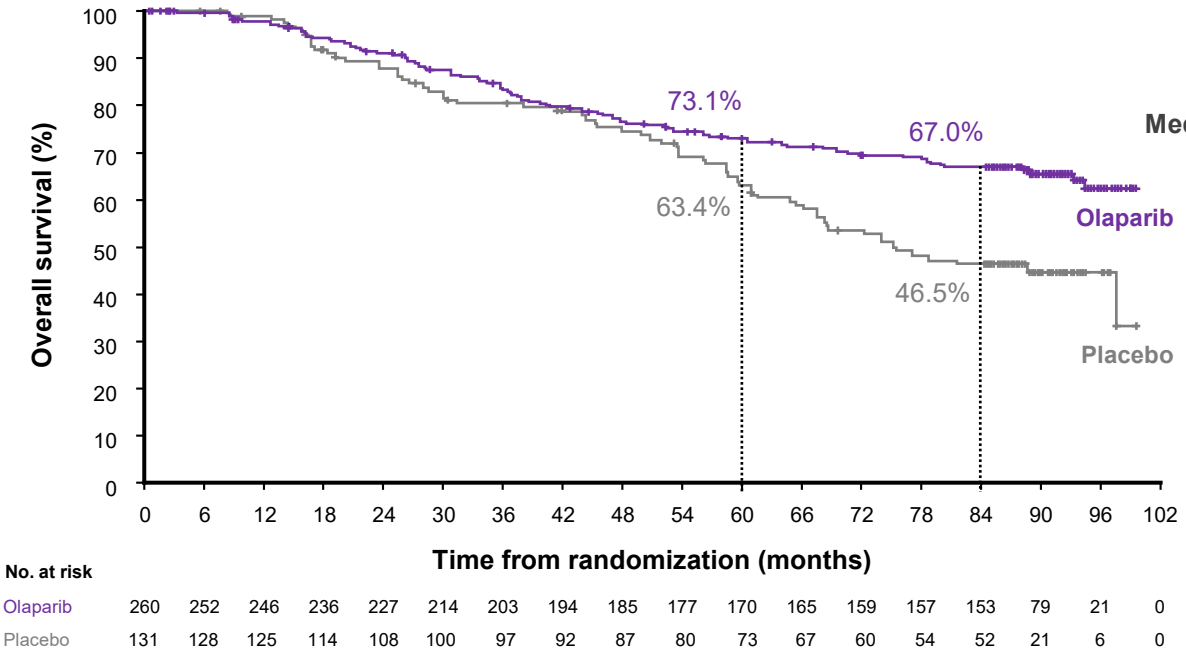
PRIME: HRp non-*BRCA*m[2]



BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; HRp, homologous recombination proficient; mo, months; NE, not estimable; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

1. González-Martín A et al. ESMO Congress 2022; Abstract 530P. 2. Li N et al. SGO Annual Meeting on Women's Cancer 2022; Abstract LBA 5. 3. Ray-Coquard I et al. ESMO Congress 2019; Abstract 3955. 4. Monk BJ et al. ASCO Annual Meeting 2022; Abstract LBA5500.

SOLO1 (GOG-3004): OS benefit of maintenance olaparib in *BRCA*m newly diagnosed ovarian cancer was sustained beyond the end of treatment (7-year follow-up data)



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

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

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

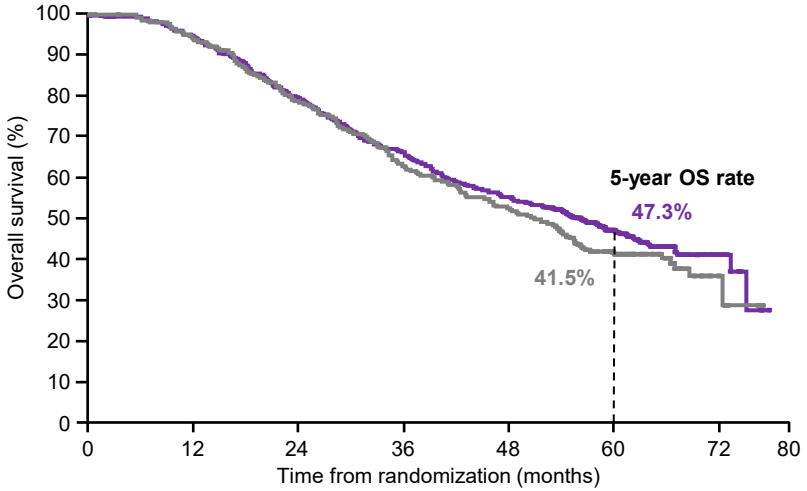
*$P<0.0001$ required to declare statistical significance

BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PARP; poly (ADP-ribose) polymerase.

DiSilvestro P et al. ESMO Congress 2022; Abstract 5170.

PAOLA-1 (ENGOT-ov25): final OS shows benefit in HRd cohort

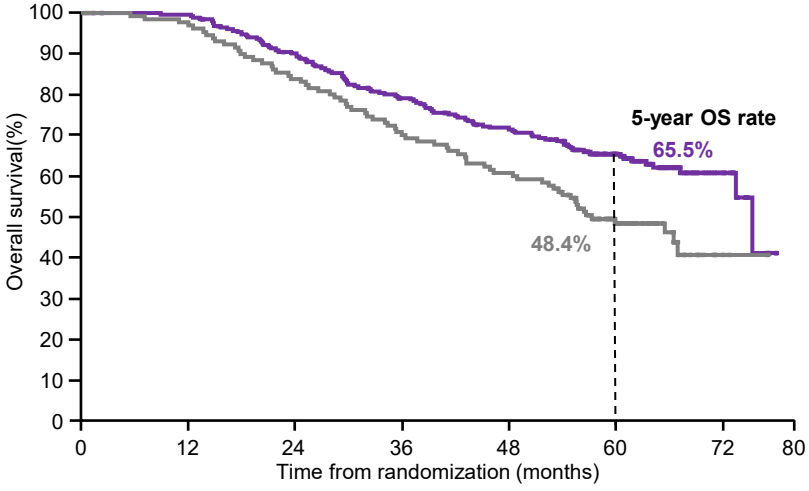
OS analysis: ITT population



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

HR: 0.92 (95% CI, 0.76–1.12)

HRD-positive[a] subgroup



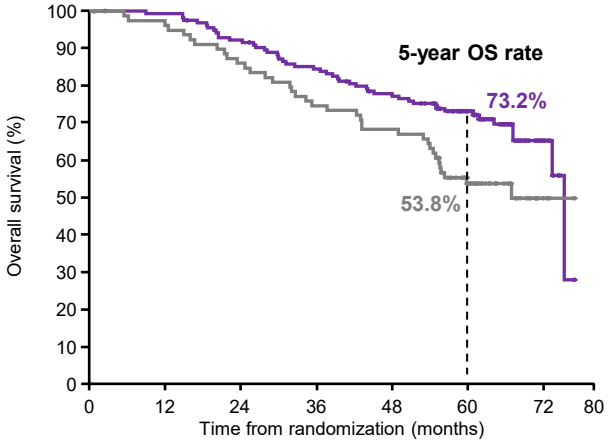
	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)[b]	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR: 0.62 (95% CI, 0.45–0.85)

[a] HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay. [b] Median unstable; <50% data maturity.
CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent to treat; OS, overall survival.
Ray-Coquard I et al. ESMO Congress 2022; Abstract LBA29.

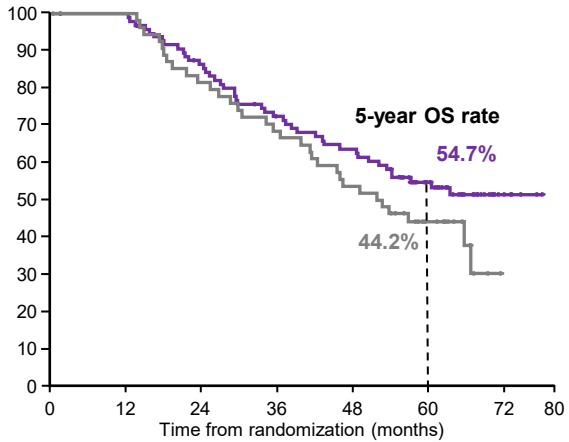
PAOLA-1 (ENGOT-ov25): OS subgroup analysis

*BRCA*m[a]



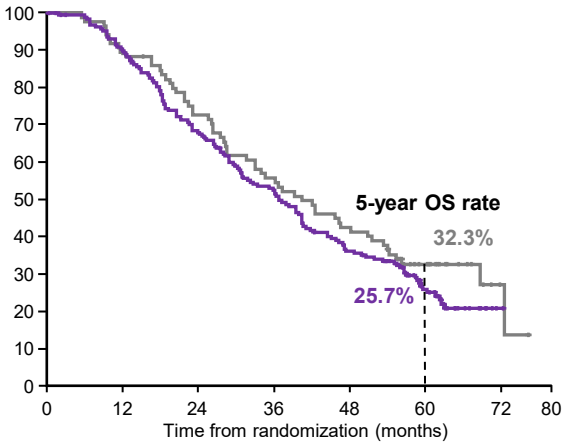
	Olaparib + bevacizumab (n=157)	Placebo + bevacizumab (n=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)[b]	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR: 0.60 (95% CI, 0.39–0.93)	

HRD-positive,[c] excluding *BRCA*m



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

HRD-negative[c]



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

[a] By central labs. [b] Unstable median. <50% data maturity. [c] By Myriad myChoice HRD Plus.
BRCA, BRCA DNA repair associated gene; BRCAm, BRCA mutated; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; OS, overall survival.
Ray-Coquard I et al. ESMO Congress 2022; Abstract LBA29.

PARPi therapy has shown OS detriment in *BRCA*m recurrent OC, leading to voluntary withdrawals of treatment indications

PARPi maintenance therapy for recurrent disease – NOVA[1]

Niraparib May 2022 (GSK, Zejula): the current OS results indicate a possible OS detriment to patients in the overall non-g*BRCA*m cohort and to patients in the non-g*BRCA*m/HRDpos subgroup who received niraparib maintenance in this setting, as compared to placebo. The reason for this is currently unknown, and additional efforts are ongoing to determine the potential etiology

PARPi treatment for *BRCA*m recurrent disease – ARIEL4[2]

Rucaparib June 2022 (Clovis Oncology, Rubraca): **Clovis Oncology has voluntarily withdrawn** Rubraca for the treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies

PARPi treatment for *BRCA*m recurrent disease – SOLO3[3]

Olaparib August 2022 (AstraZeneca, Lynparza): **AstraZeneca has voluntarily withdrawn** the Lynparza indication for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy

PARPi treatment for HRD-positive recurrent disease – QUADRA[4]

Niraparib September 2022 (GSK, Zejula): **the voluntary withdrawal of this indication** is based on a totality of information from PARP inhibitors in the late line treatment setting in ovarian cancer. A potential detrimental effect on overall survival was observed with other (non-GSK) PARP inhibitors in two independent randomized, active-controlled clinical trials conducted in a *BRCA* mutant 3L+ advanced ovarian cancer population

BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; g*BRCA*m, germline *BRCA* mutated; HRD, homologous recombination deficiency; OC, ovarian cancer; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; pos, positive.

1. GlaxoSmithKline. Accessed August 23, 2022. https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%20(niraparib)%20Dear%20HCP%20Letter.pdf/ 2. Clovis Oncology. Accessed August 23, 2022. https://clovisoncology.com/pdfs/US_DHCPL_final_signed.pdf/ 3. AstraZeneca. Accessed August 31, 2022. https://www.lynparzahcp.com/content/dam/physician-services/us/590-lynparza-hcp-branded/hcp-global/pdf/solo3-dhcp-final-signed.pdf/ 4. GlaxoSmithKline. Accessed September 19, 2022. https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%20(niraparib)%20Dear%20HCP%20Letter%20September%202022.pdf

Summary

- Bevacizumab and PARPi maintenance therapy have shown PFS prolongation in newly diagnosed ovarian cancer[1–7]
- The greatest benefit of PARPi maintenance is observed in patients with *BRCA*m or HRd disease, which accounts for approximately 20% and 50% of patients, respectively[6,8]
- There has been no overall survival benefit associated with PARPi maintenance or treatment in the recurrent disease setting[9–11]
- Recent OS data have shown benefit associated with PARPi maintenance in the 1L setting, with the greatest effect seen in *BRCA*m and HRd cohorts and no benefit seen in HRp cohorts[12,13]

1L, first line; *BRCA*, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473–2483. 2. Perren TJ et al. *N Engl J Med*. 2011;365(26):2484–2496. 3. Monk BJ et al. SGO Annual Meeting on Women's Cancer 2020; Presentation 31. 4. Li N et al. SGO Annual Meeting on Women's Cancer 2022; Abstract LBA 5. 5. Bradley W et al. SGO Virtual Annual Meeting on Women's Cancer 2021; Abstract 10520. 6. Ray-Coquard I et al. ESMO Congress 2019; Abstract LBA2_PR. 7. Monk BJ et al. ASCO Annual Meeting 2022; Abstract LBA5500. 8. Konstantinopoulos PA et al. *Cancer Discov*. 2015;5(11):1137–1154. 9. GlaxoSmithKline. Accessed Sep 27, 2022. https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%20(niraparib)%20Dear%20HCP%20Letter.pdf/ 10. Clovis Oncology. Accessed Sep 27, 2022. https://clovisoncology.com/pdfs/US_DHCPL_final_signed.pdf/ 11. AstraZeneca. Accessed Sep 27, 2022. https://www.lynparzahcp.com/content/dam/physician-services/us/590-lynparza-hcp-branded/hcp-global/pdf/solo3-dhcp-final-signed.pdf/ 12. DiSilvestro P et al. ESMO Congress 2022; Abstract 5170. 13. Ray-Coquard I et al. ESMO Congress 2022; Abstract LBA29.