EVOLUTION OF PARP INHIBITOR USE IN OVARIAN CANCER

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Department of Gynecology and Obstetrics

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

DISCLOSURES

EMORY UNIVERSITY SCHOOL OF MEDICINE
Department of Gynecology and Obstetrics

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

- I receive a stipend as EIC of *Gynecologic Oncology Reports*
- I have done one consulting board for Eisai and have received stipends for nonbranded talks for OncLive and Curio sponsored conferences
- Our division has received clinical trial funding support from multiple companies (Ergomed, Gilead, Corcept, and Mersana)
- Borrowed slides from multiple colleagues around the country including Dr. Christine Walsh, Dr. Jubilee Brown and Dr. Rob Coleman.

U.S. FEMALE CANCER STATISTICS 2024

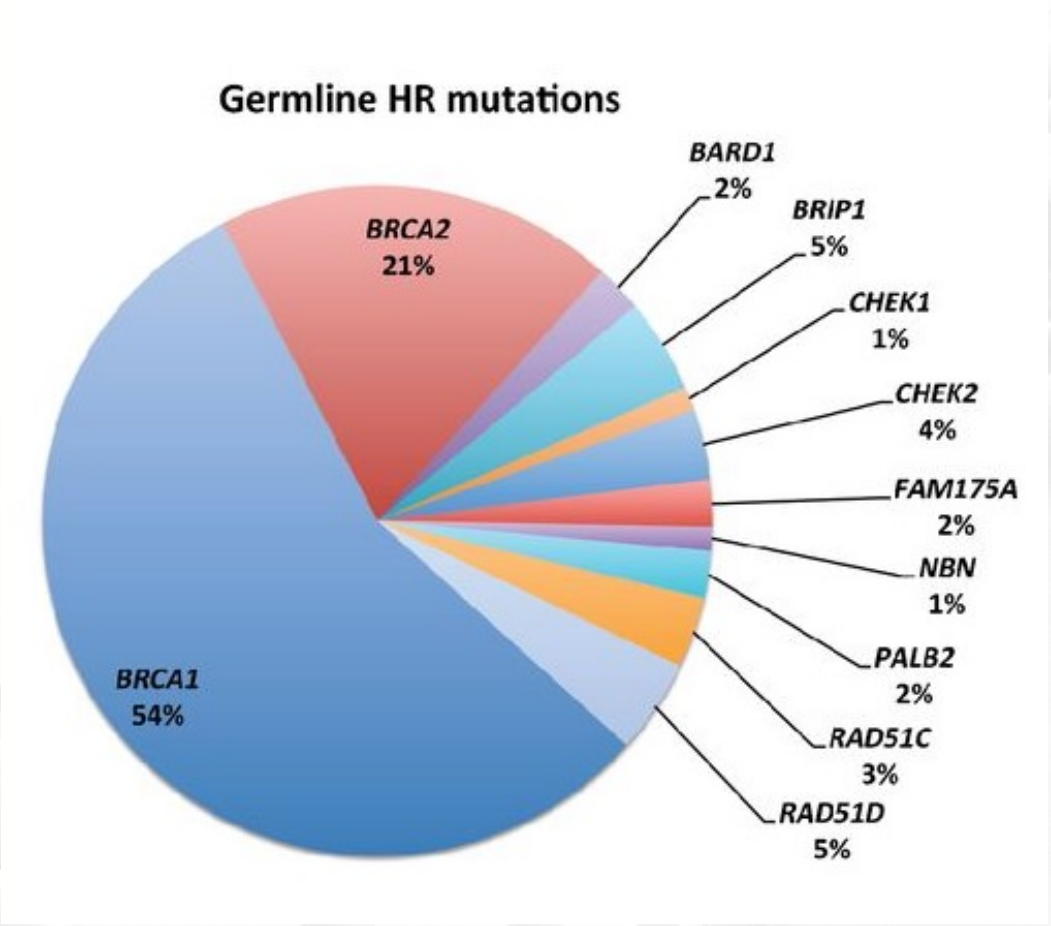
Site	Number	Deaths
Breast	310,720	42,250
Uterus	67,880	13,250
Ovary	19,680	12,740
Cervix	13,820	4,360
Vulva	6,900	1,630

American Cancer Society. Cancer Facts and Figures 2024

OBJECTIVES

- To outline trial results on PARP inhibitors in ovarian cancer in upfront therapy
- To discuss implementation of PARP inhibitors
- To understand recent publications, dear investigator letters and changing recommendations for use of PARP inhibitors in the recurrent ovarian cancer space

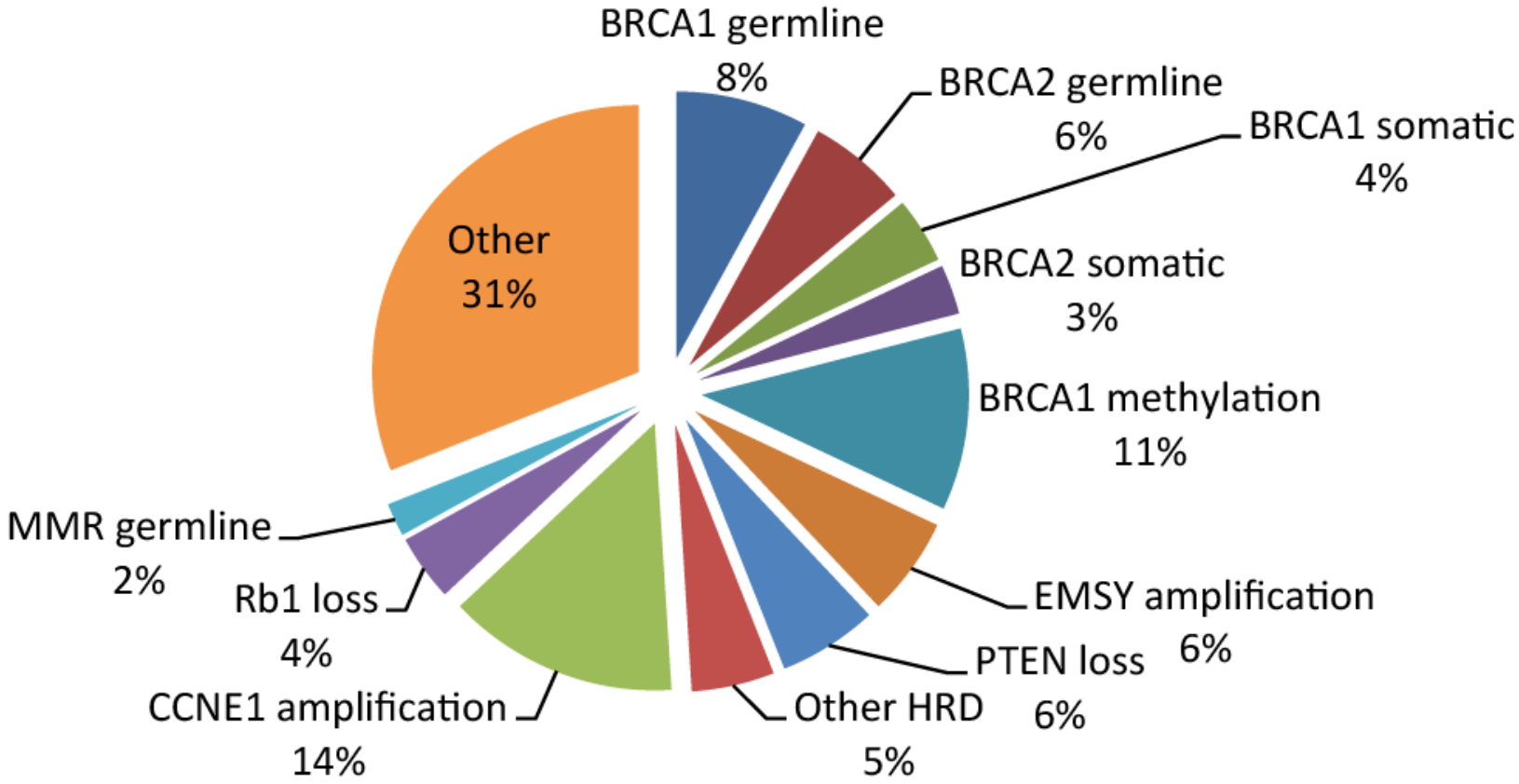
GERMLINE MUTATIONS ACCOUNT FOR ≈ 24% OF OVARIAN CANCERS



- Most ovarian cancer is still sporadic (70-80%)
- BRCA1 and BRCA2 account for majority of germline mutations (75%)
- Lynch syndrome is other main group (NOT HR)
- Other homologous recombination genes

Pennington KP et al. Clin Cancer Res 2014; 20(3): 764-775

Molecular Profiling of Serous Ovarian Cancer



- 24% Germline and 9% Somatic mutations in HRD genes
- 50% of serous cancers are HRD!

Credit: R. Arend; Cancer Genome Atlas Research, Nature. 2011;474:609

OVARIAN CANCER CONVENTIONAL TREATMENT

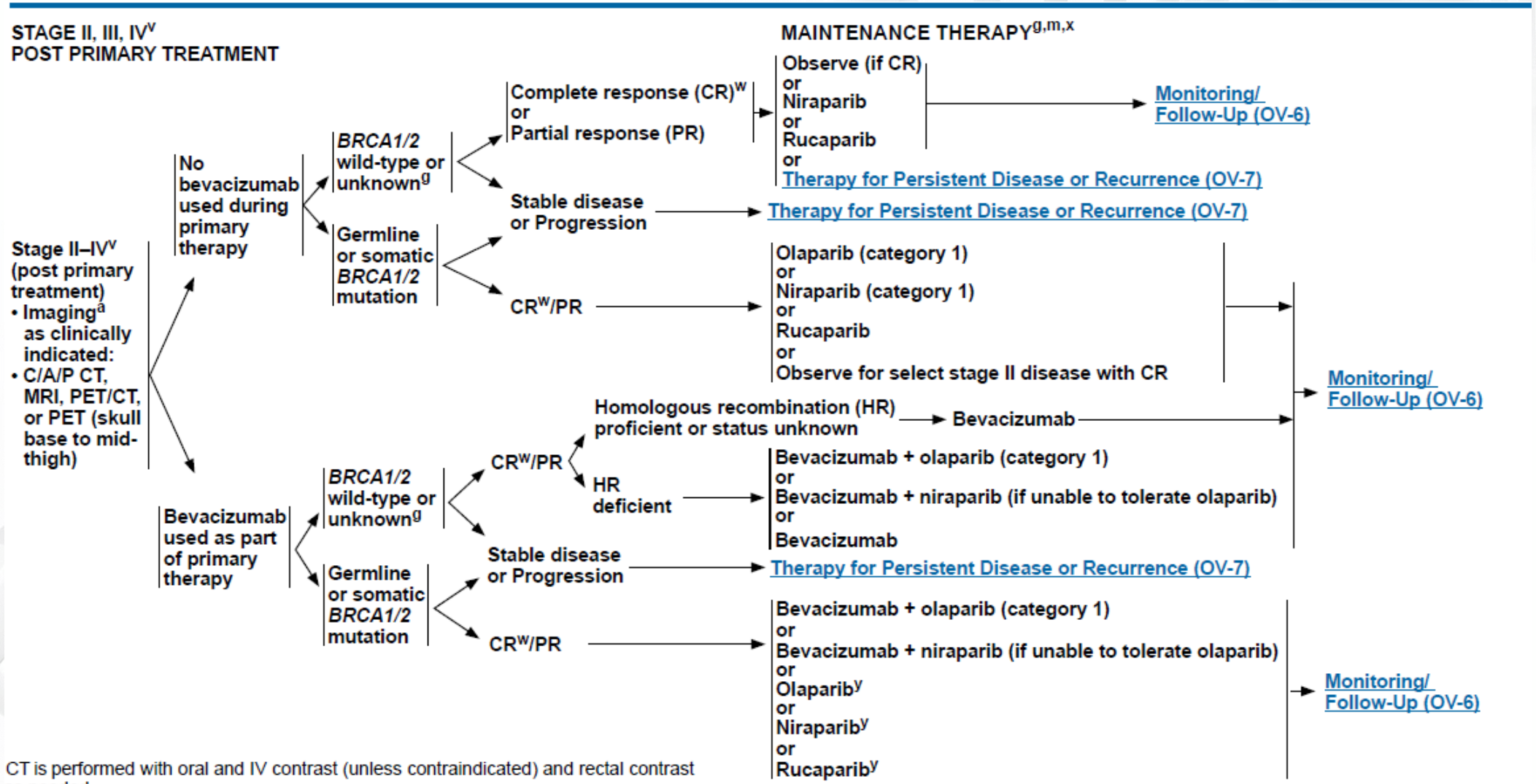
1. Tumor reductive surgery followed by chemotherapy versus neoadjuvant chemotherapy with an interval debulking
   - Surgical goal to reduce tumor to microscopic or at least to under 1 cm in terms of largest remaining lesions (R0 vs. R1)

2. Adjuvant Chemotherapy (except in rare Stage I patients)
   - Combination chemotherapy with taxane/platinum agent +/- bevacizumab
   - Intraperitoneal or HIPEC chemotherapy in selected patients

3. Maintenance therapy (PARP inhibitor and/or bevacizumab) in selected patients (some advocate ALL patients)

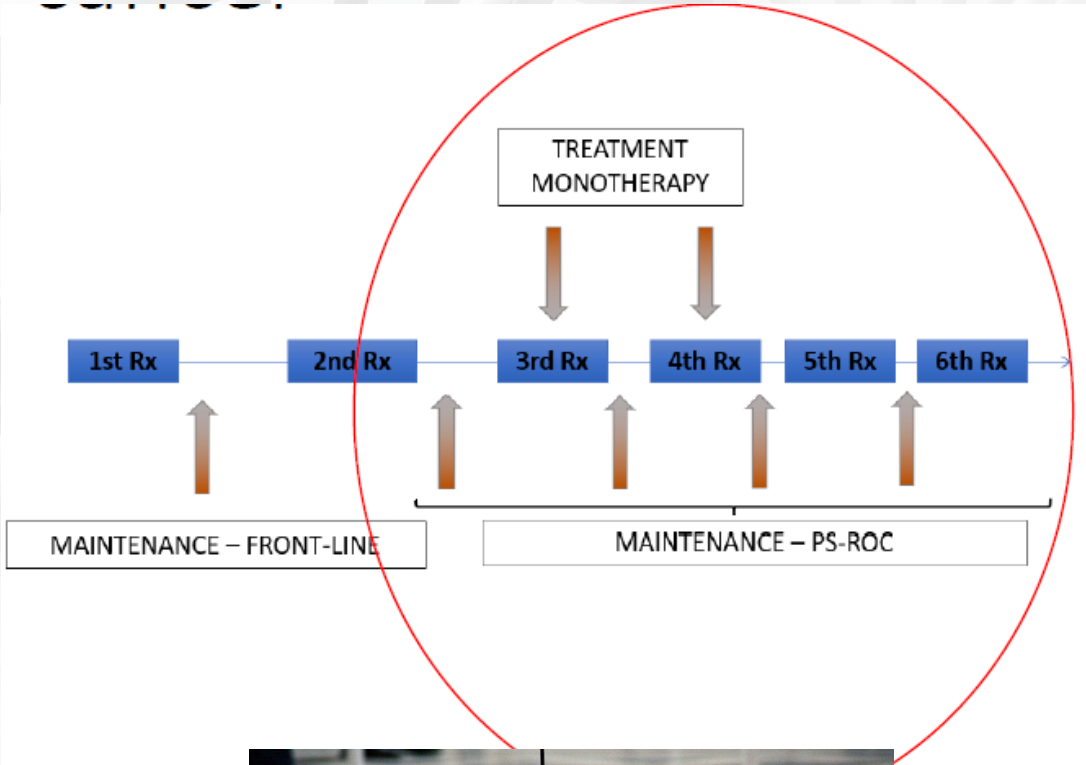
4. Clinical trial if available

CURRENT NCCN MAINTENANCE GUIDELINES FOR OVARIAN CANCER



PARP INHIBITOR USE IN OVARIAN CANCER

- December 2014-May 2020
  - Nine FDA approvals for PARP inhibitors in ovarian cancer
    - Maintenance after frontline treatment
    - Monotherapy for recurrent ovarian cancer
    - Maintenance after treatment for recurrent platinum sensitive ovarian cancer
  - May 2022 to the present
    - A series of Dear Health Care Provider Letters with withdrawals and restrictions to prior approvals



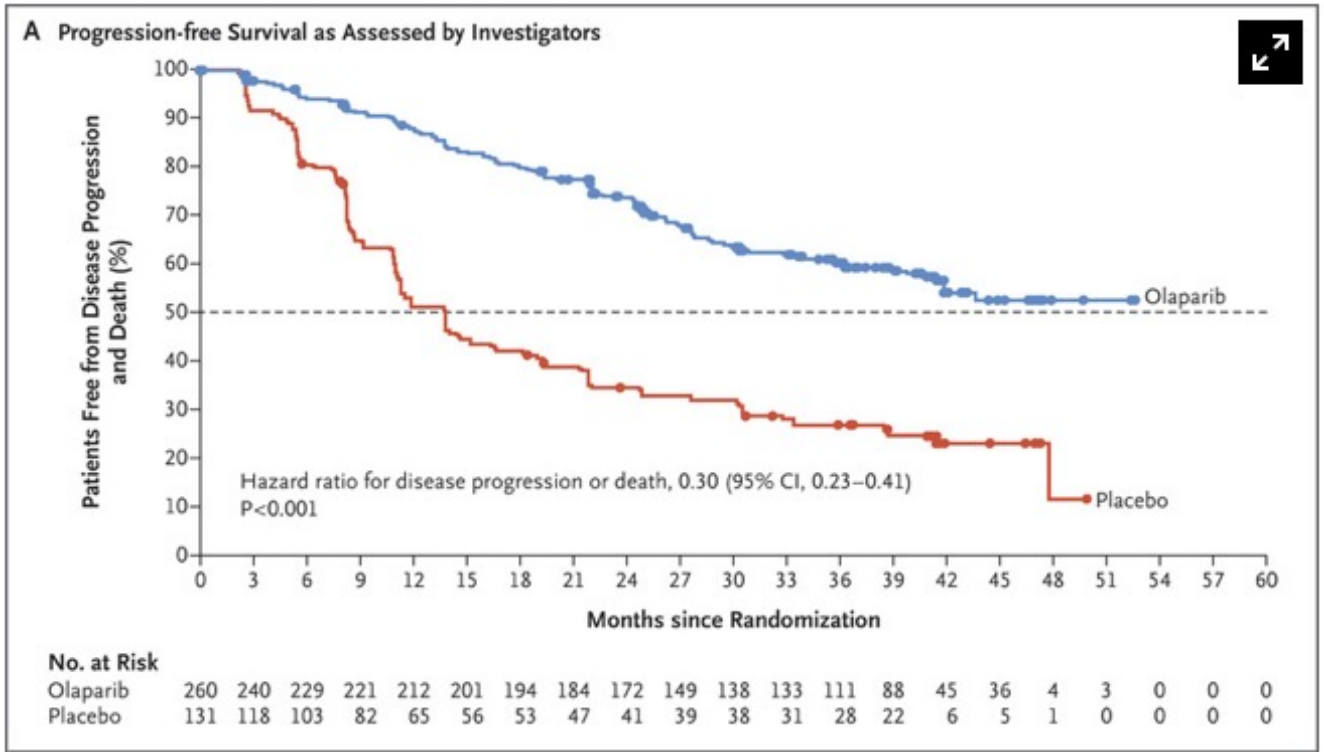
RESULTS OF THE PARP MAINTENANCE TRIALS

	SOLO-1 (Olaparib)	PAOLA-1 (Olaparib + Bev)	PRIMA (Niraparib)	PRIME (Niraparib)	ATHENA (Rucaparib)
ITT		22.1 vs. 16.6 **HR: 0.59**	13.8 v 8.2 **HR: 0.62**	24.8 vs 8.3 **HR: 0.45**	20.2 vs 9.2 **HR: 0.52**
BRCA-mt	56.0 vs 13.8 **HR: 0.33**	37.2 vs 21.7 **HR: 0.31**	22.1 vs 10.9 **HR: 0.40**	NR vs 10.8 **HR: 0.40*** *BRCA population is gBRCA only	NR vs 14.7 **HR: 0.40**
HRD-Test Positive		37.2 vs 17.7 **HR: 0.33**	21.9 vs 10.4 **HR: 0.43**	24.8 vs 11.1 **HR: 0.58*** *BRCA population is gBRCA only	28.7 vs 11.3 **HR: 0.47**
HRD/BRCA-wt		28.1 vs 16.6 **HR: 0.43**	19.6 vs 8.2 **HR: 0.50**	NR	NR
HRD-Test Negative		16.6 vs 16.2 **HR: 1.0**	8.1 vs 5.4 **HR: 0.68**	14.0 vs 5.5 **HR: 0.41**	12.1 vs 9.1 **HR: 0.65**
Median Follow-up	57.6 mos	27.4	13.8	27.5	NR

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

Kathleen Moore, M.D., Nicoletta Colombo, M.D., Giovanni Scambia, M.D., Byoung-Gie Kim, M.D., Ph.D., Ana Oaknin, M.D., Ph.D., Michael Friedlander, M.D., Alla Lisyanskaya, M.D., Anne Floquet, M.D., Alexandra Leary, M.D., Gabe S. Sonke, M.D., Ph.D., Charlie Gourley, M.D., Ph.D., Susana Banerjee, M.D., Ph.D., et al.

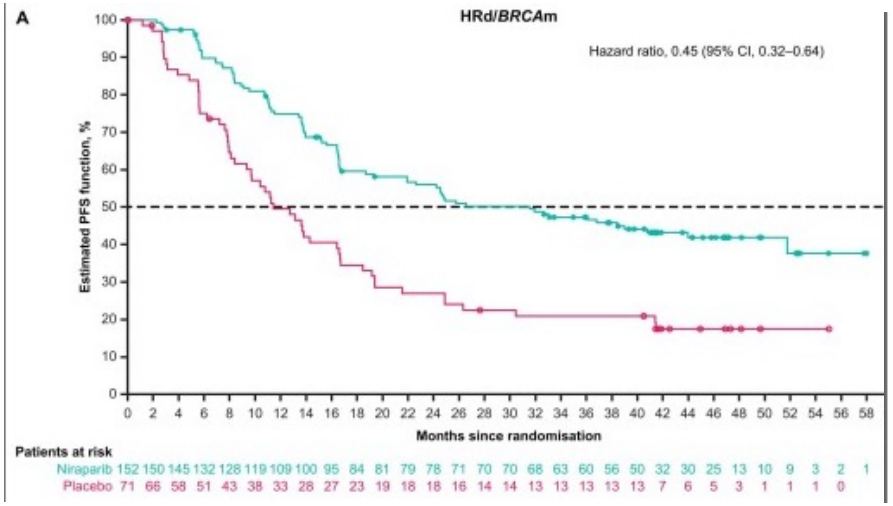
- Hazard ratio of disease progression or death: 0.3
- Patients with germline or somatic *BRCA1/2* mutations
- "SOLO-1"
- International superiority trial showed 70% reduction in risk
- Updated 7 year overall survival still favors olaparib 67% vs 46% (HR-0.55)



Moore K et al, New Engl J Med 2018
DiSilvestro P et al, JCO 2022

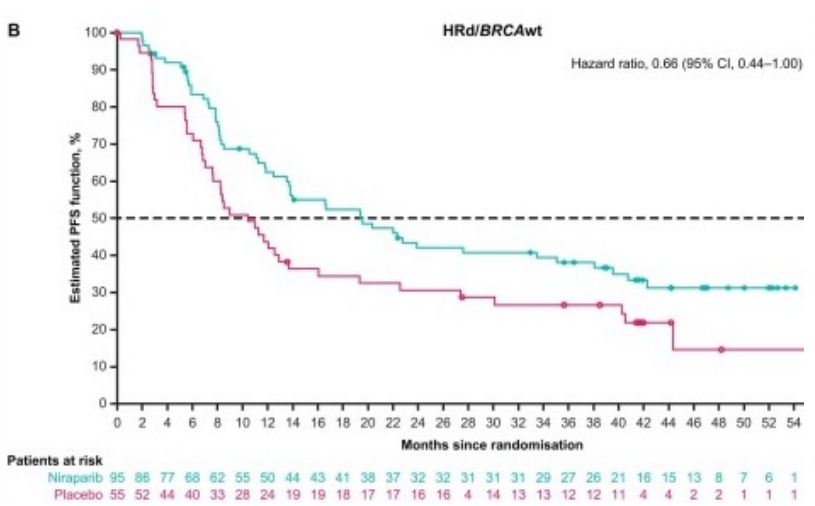
PRIMA (UPDATED): PFS SUBGROUPS

HRd.BRCAm



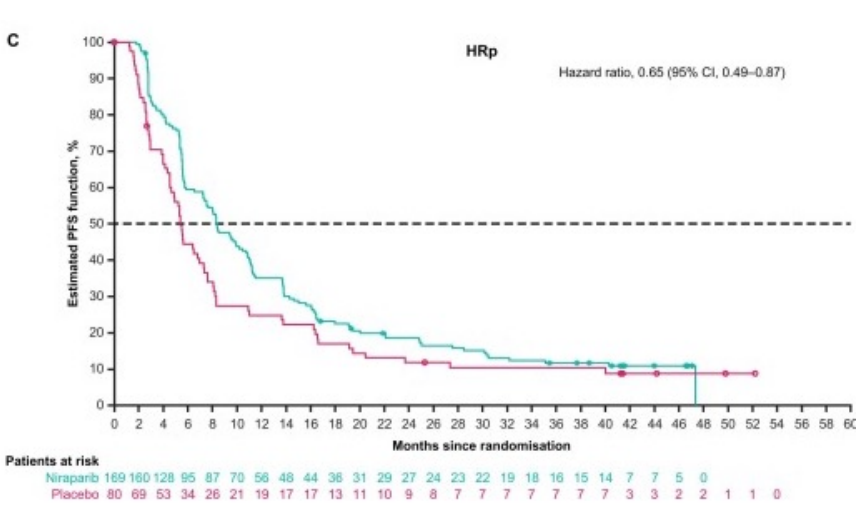
- Median PFS: 31.5 vs 11.5 months
- HR 0.45

HRd.BRCAwt



- Median PFS: 19.4 vs 10.4 m
- HR 0.66

HRproficient



- Median PFS: 8.4 vs 5.4 m
- HR 0.65

Gonzalez-Martin A, Eur J Cancer 2023; 189

OLAPARIB PLUS BEVACIZUMAB FIRST-LINE MAINTENANCE IN OVARIAN CANCER: FINAL OVERALL SURVIVAL RESULTS FROM THE PAOLA-1/ENGOT-OV25 TRIAL

I. Ray-Coquard et al.

Annals of Oncology

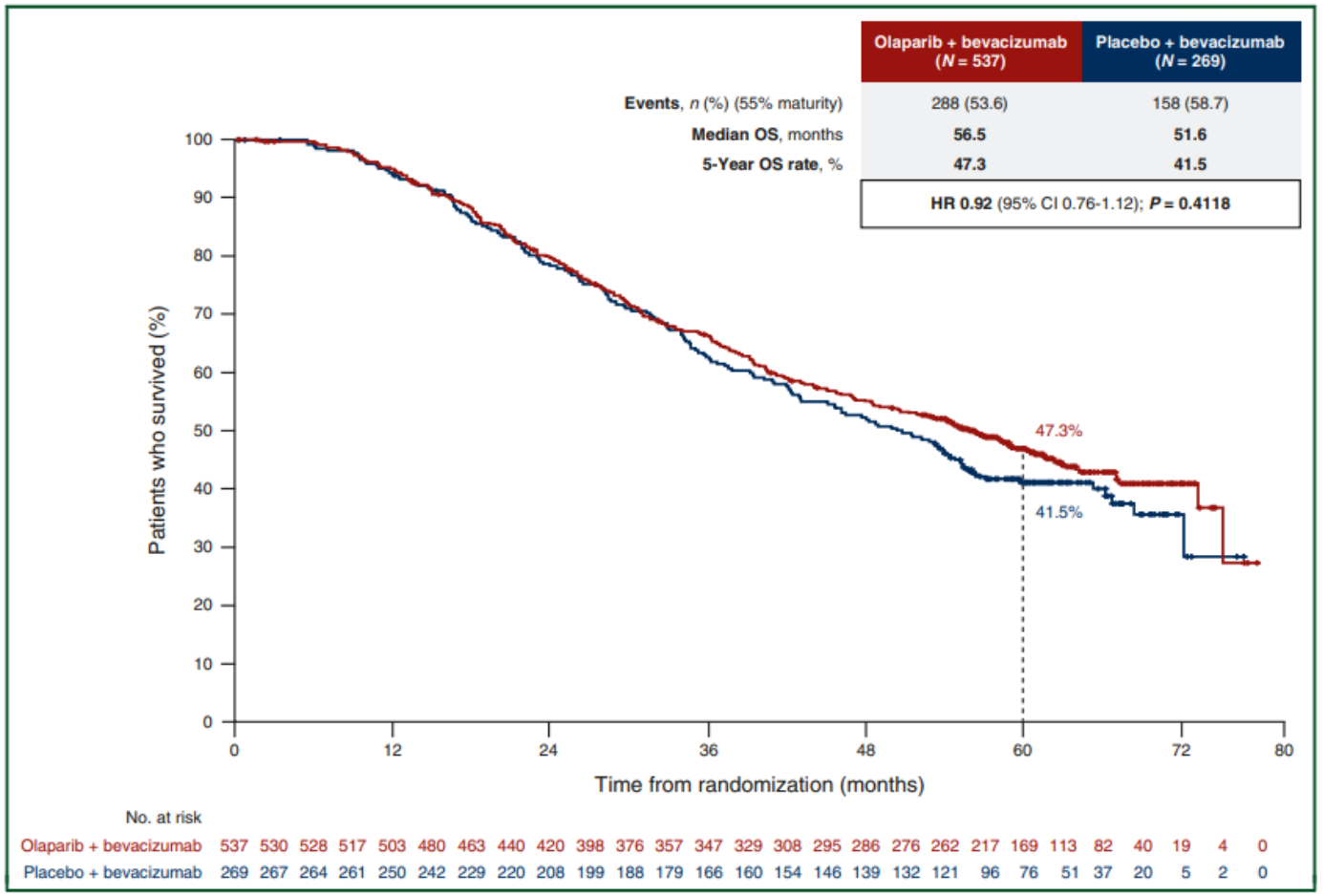
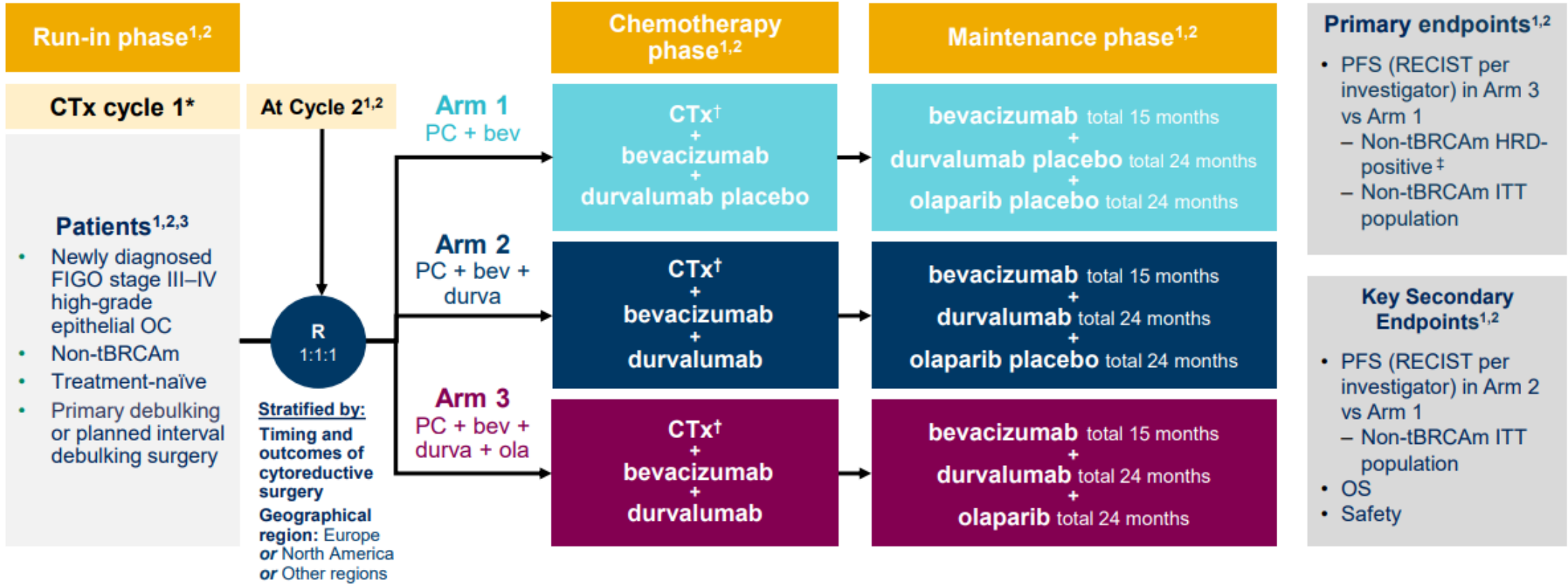


Figure 1. Kaplan–Meier estimates of overall survival in the intention-to-treat population. Shown are Kaplan–Meier estimates of the rate of freedom from death. CI, confidence interval; HR, hazard ratio; OS, overall survival.

Conclusions: Olaparib plus bevacizumab provided clinically meaningful OS improvement for **first-line patients with HRD** positive ovarian cancer

DUO-O, a placebo-controlled, double-blind study, investigates the efficacy and safety of PC + bevacizumab + durvalumab followed by maintenance therapy with bevacizumab + durvalumab + olaparib in patients with newly diagnosed non-tBRCAm advanced OC[1,2,3]



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. *With or without bevacizumab according to local practice; †Cycles 2–6; ‡ Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay; §Safety criteria required to be met for entry into the maintenance phase. Abbreviations in slide notes.

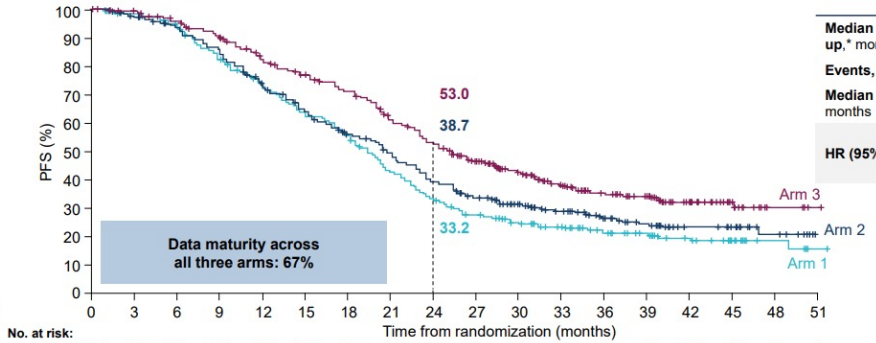
49 1. Harter P, et al. Presented at ASCO Annual Meeting 2023. 2-6 June. Chicago, Illinois.2. Harter P, et al. Presented at SCO Annual Meeting 2024. March 16-18. San Diego, California. 2. NCT03737643. Available at: https://clinicaltrials.gov/ct2/show/study/NCT03737643 (Accessed March 2024)

DUO-O

Final PFS for non-tBRCAm ITT patients in the 1L setting

DCO-2 September 18, 2023

Arm 1 vs Arm 2 & 3



	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	34.5	33.1	32.0
Events, n (%)	283 (75)	257 (69)	221 (58)
Median PFS,† months	19.3	20.6	25.1
HR (95% CI)‡		0.87 (0.74-1.03) p=0.11§	0.61 (0.51-0.73)

No. at risk:

Arm 1	378	363	341	297	260	223	196	150	117	95	77	65	50	42	27	15	6	1
Arm 2	374	354	335	302	255	222	190	161	130	109	87	71	54	43	27	16	8	0
Arm 3	378	367	352	324	287	267	244	205	178	144	116	87	70	56	35	18	5	1

*In censored patients; †Medians and rates were estimated by the KM method (medians are unstable in arms with <50% maturity); ‡HRs and CIs were estimated from a stratified Cox PH model. Model was stratified by timing and outcome of cytoreductive surgery for the non-tBRCAm HRD-positive population, and by timing and outcome of cytoreductive surgery and geographic region for the non-tBRCAm ITT population, all vs. Arm 1; §*P* value was calculated from a stratified log-rank test. Statistical significance for Arm 3 versus Arm 1 was achieved at the interim PFS analysis in both the non-tBRCAm HRD-positive (DCO1 = December 5, 2022; HR 0.49 [95% CI 0.34–0.69]; *P*<0.0001) and non-tBRCAm ITT (DCO1 = December 5, 2022; HR 0.63 [95% CI 0.52–0.76]; *P*<0.0001) populations; the updated analysis (DCO2) is descriptive in nature for Arm 3 versus Arm 1, so no *P* value is reported. The comparison of Arm 2 versus Arm 1 in the non-tBRCAm HRD-positive population was not part of the predefined MTP and so was not formally tested. The comparison of Arm 2 versus Arm 1 was not statistically significant at the time of the interim PFS analysis and so was retested at the final PFS analysis; the boundary for declaring statistical significance at the final PFS analysis was 0.0248 (Arm 2 vs Arm 1) for 2.5% alpha. MTP, multiple-testing procedure.

Abbreviations in slide notes.

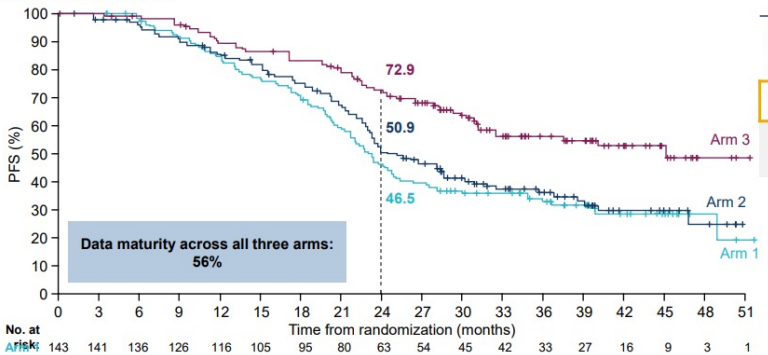
56 Harter P, et al. Presented at SGO Annual Meeting 2024. March 16-18. San Diego, California.

- PFS only significantly better with both durvalumab and olaparib
- Unsurprisingly, biggest impact in HRD population

Longest observed mPFS in Arm 3 for non-tBRCAm HRD-positive patients in the 1L setting – Final PFS results

DCO-2 September 18, 2023

Arm 1 vs Arm 2 & 3



	Arm 1 PC + Bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Median follow-up,* months	38.4	33.1	34.6
Events, n (%)	94 (66)	89 (60)	57 (41)
Median PFS,† months	23.3	25.1	45.1
HR (95% CI) vs Arm 1‡		0.89 (0.67-1.19)§	0.46 (0.33-0.65)

No. at risk:

Arm 1	143	141	136	126	116	105	95	80	63	54	45	42	33	27	16	9	3	1
Arm 2	148	142	136	128	118	112	102	89	68	59	45	36	29	22	13	9	5	0
Arm 3	140	138	135	131	120	116	111	103	94	82	66	50	41	35	22	13	3	1

*In censored patients; †Medians and rates were estimated by the KM method (medians are unstable in arms with <50% maturity); ‡HRs and CIs were estimated from a stratified Cox PH model. Model was stratified by timing and outcome of cytoreductive surgery for the non-tBRCAm HRD-positive population, and by timing and outcome of cytoreductive surgery and geographic region for the non-tBRCAm ITT population; §the updated analysis (DCO2) is descriptive in nature for Arm 3 versus Arm 1, so no *P* value is reported. The comparison of Arm 2 versus Arm 1 in the non-tBRCAm HRD-positive population was not part of the predefined MTP and so was not formally tested. The comparison of Arm 2 versus Arm 1 was not statistically significant at the time of the interim PFS analysis and so was retested at the final PFS analysis; the boundary for declaring statistical significance at the final PFS analysis was 0.0248 (Arm 2 vs Arm 1) for 2.5% alpha. MTP, multiple-testing procedure.

Abbreviations in slide notes.

55 Harter P, et al. Presented at SGO Annual Meeting 2024. March 16-18. San Diego, California.

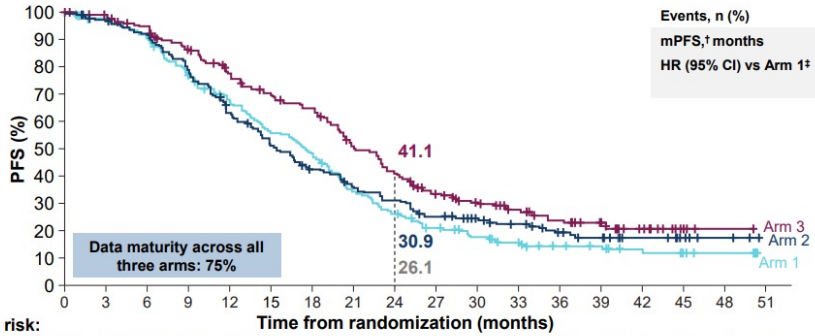
024

Unstratified Subgroup Analysis of HRD-negative Subpopulation – Final PFS (predefined)

DCO-2 September 18, 2023; HRD-negative subpopulation

Preplanned Exploratory Analysis

Arm 1 vs Arm 2 & Arm 3;



	Arm 1 PC + B N=216	Arm 2 PC + B + D N=199	Arm 3 PC + B + D + O N=211
Median follow-up,* months	31.0	34.1	30.2
Events, n (%)	173 (80)	152 (76)	144 (68)
mPFS,† months	17.5	15.4	21.1
HR (95% CI) vs Arm 1‡		0.92 (0.74–1.14)	0.68 (0.54–0.85)

No. at risk:

Arm 1	216	203	188	159	135	12	97	68	52	39	30	22	16	14	10	6	3	0
Arm 2	199	189	177	153	120	97	78	65	56	44	37	31	23	19	13	6	3	0
Arm 3	211	203	191	170	146	133	121	93	76	57	47	36	29	21	13	5	2	0

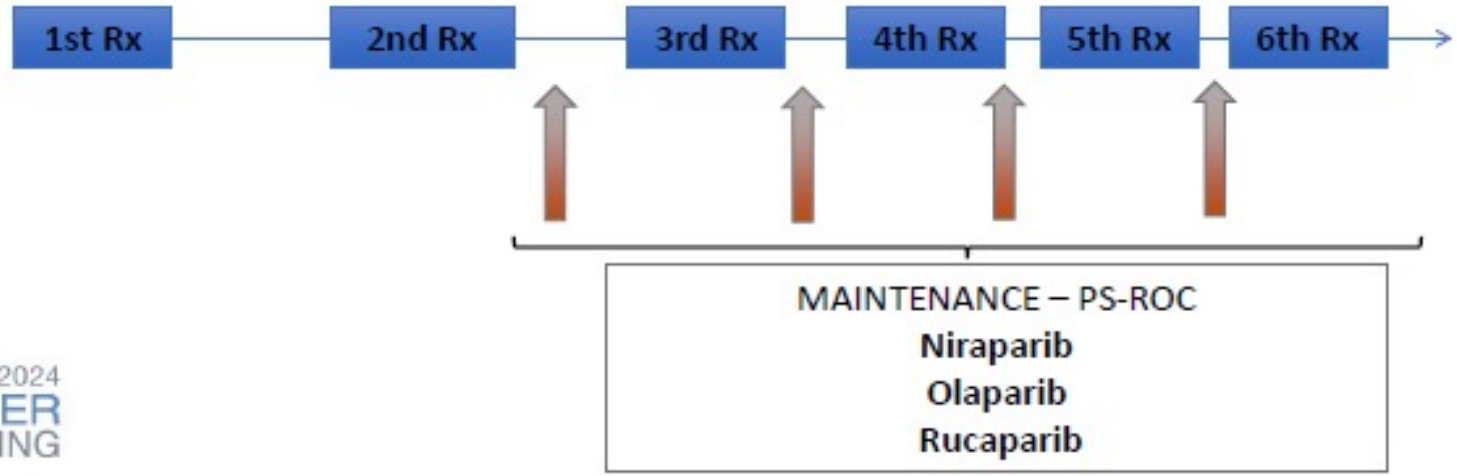
*In censored patients; †Medians and rates were estimated by the KM method (medians are unstable in arms with <50% maturity); ‡HRs and CIs were estimated from an unstratified Cox PH model

Abbreviations in slide notes.

57 Harter P, et al. Presented at SGO Annual Meeting 2024. March 16-18. San Diego, California.

MAINTENANCE AFTER TREATMENT OF PLATINUM SENSITIVE RECURRENT OVARIAN CANCER

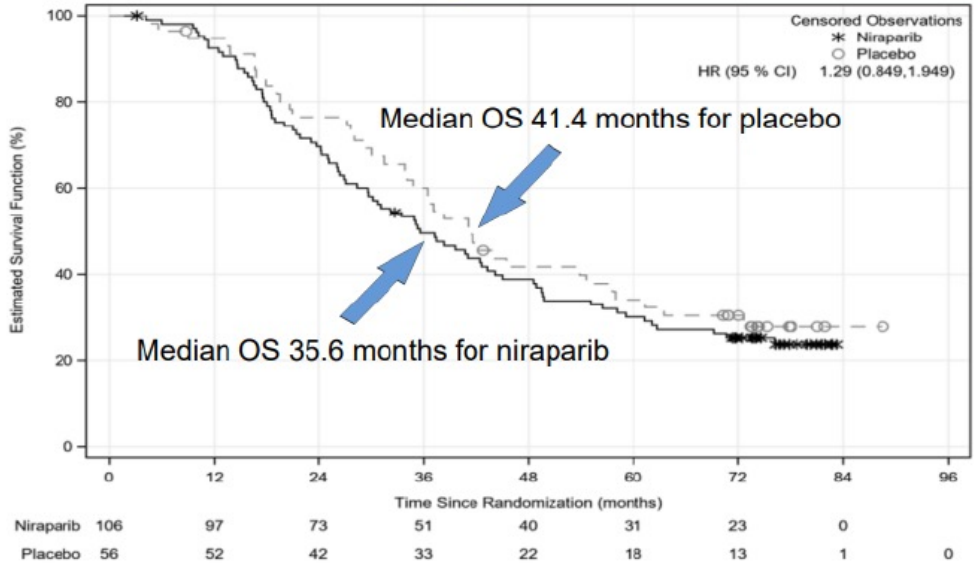
- 3/2017 – niraparib – all
- 8/2017 – olaparib – all
- 4/2018 – rucaparib – all



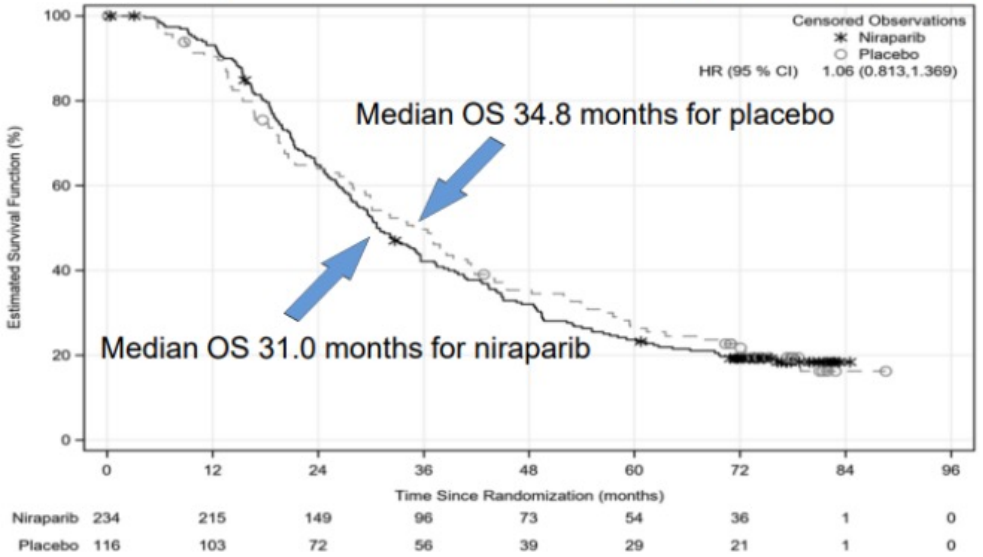
SGO 2024 WINTER MEETING

DATA SHOWING ABOUT POTENTIAL WORSE OUTCOMES FOR BRCA GERMLINE WILDTYPE PATIENTS

OS Kaplan Meier curve for the non-g*BRCA*mut HRD positive subgroup



OS Kaplan Meier curve for the non-g*BRCA*mut cohort



Data cutoff of 3/31/2021 – OS detriment to patients in non-gBRCAmut and non-gBRCAmut/HRD+ cohorts

Non-gBRCA, HRD+:	mOS 35.6 vs 41.4 months, HR 1.29 (0.85 – 1.95)
Non-gBRCA, overall:	mOS 31.0 vs 34.8 months, HR 1.06 (0.81 – 1.37)
gBRCA+:	mOS 40.9 vs 38.1 months, HR 0.85 (0.61 – 1.20)

Nov 2022 - Company restricts indication for niraparib second-line maintenance to gBRCA+ population

November 2022

IMPORTANT PRESCRIBING INFORMATION

Subject: (niraparib) Important Prescribing Information for the maintenance treatment of adult patients with non-g*BRCA*mut recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy in second or later line setting.

Dear Health Care Provider:

This letter is an update to the DHCP Letter dated May 2022. This letter is to inform you that, at the request of the FDA, we will restrict the indication of (niraparib) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy received in the second or later line setting **to the g*BRCA*mut patient population only;** GSK is in discussions with the FDA to update the USPI

Nov 14, 2022 – FDA requests Company to voluntarily limit rucaparib maintenance to BRCA+ patients

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 OR 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): November 14, 2022

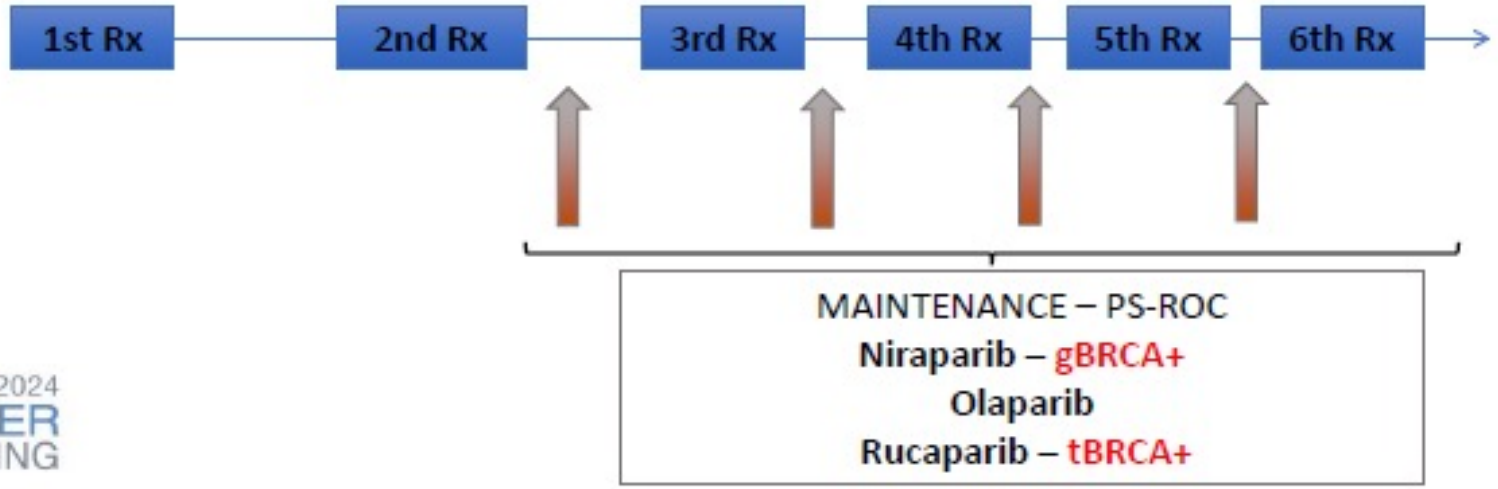
On November 14, 2022, at the request of the FDA, (the "Company") met by teleconference with the FDA to discuss the overall survival (OS) data from the Company's ARIEL3 clinical trial. The ARIEL3 dataset formed the basis for the approval of rucaparib in the US in April 2018 and in Europe in January 2019 respectively, as second-line maintenance treatment in adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. The Company submitted final OS data, including in exploratory subgroups, from the ARIEL3 study to the FDA in September 2022. The FDA requested that the Company voluntarily revise the label to limit the indication of rucaparib this second-line maintenance treatment to tBRCA patients only. The FDA further indicated to the Company that if an agreement could not be reached on the revised indication, the FDA would convene an ODAC meeting to review this matter. The Company is currently evaluating FDA's request.

SGO 2024 WINTER MEETING

SGO Society of Gynecologic O

MAINTENANCE AFTER TREATMENT OF PLATINUM SENSITIVE RECURRENT OVARIAN CANCER

- 3/2017 – niraparib – ~~all~~ → 11/2022 restricted to gBRCAmut
- 8/2017 – olaparib – all
- 4/2018 – rucaparib – ~~all~~ → 12/2022 restricted to tBRCAmut

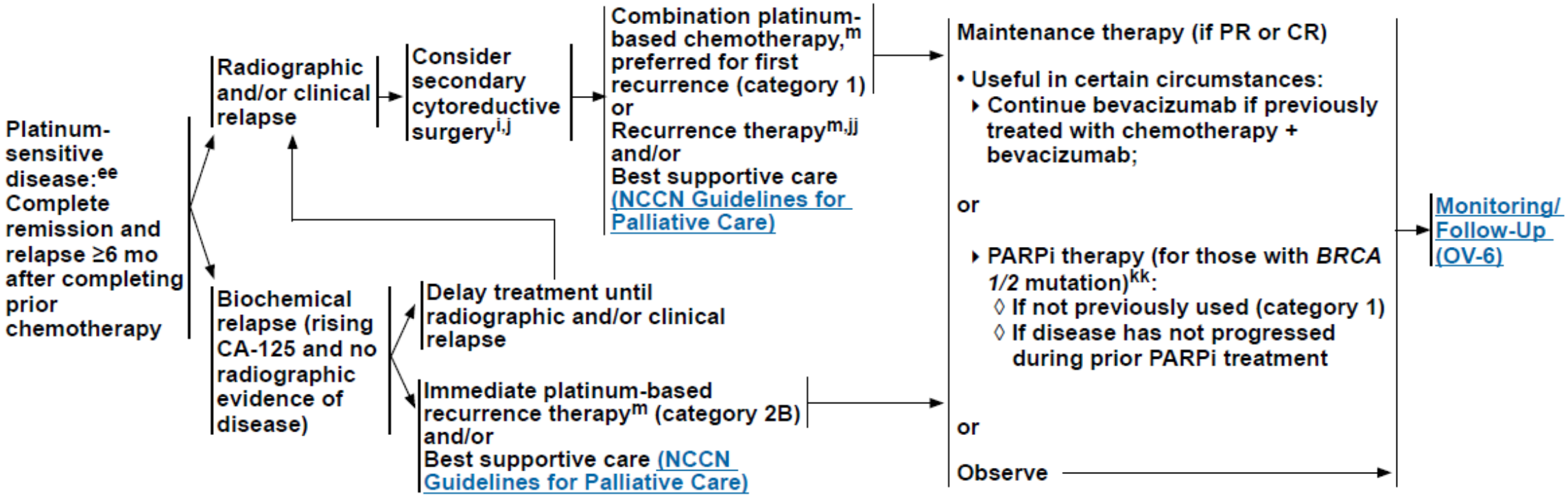


SGO 2024 WINTER MEETING

NCCN Guidelines Version 1.2024
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

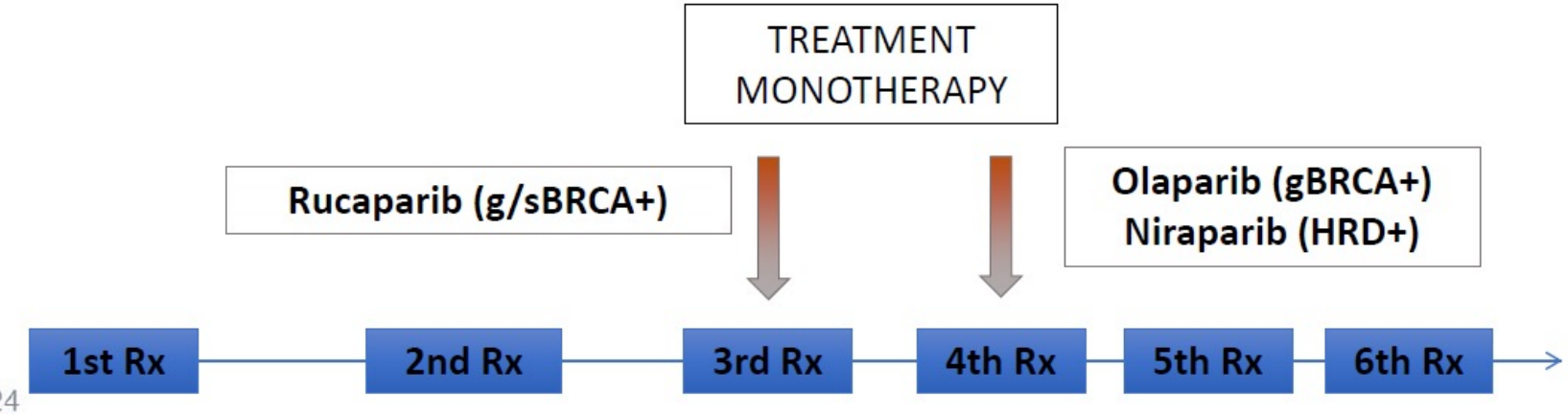
DISEASE STATUS[e,cc,dd]

RECURRENCE THERAPY FOR PLATINUM-SENSITIVE DISEASE[m,ff,gg,hh]



Monotherapy for Recurrent Ovarian Cancer

- 12/2014 – olaparib – gBRCA+ ROC
- 12/2016 – rucaparib – g/sBRCA+ ROC
- 10/2019 – niraparib – HRD+ ROC



SGO 2024 WINTER MEETING

Society of Gynecologic Oncology

SOLO-3

	Olaparib N=178	TPC N=88
PFS2		
Number (%) of events	114 (64)	48 (55)
Median PFS2, months	23.6	19.6
HR (95% CI)	0.80 (0.56–1.15)	
P value	0.229	
OS		
Number (%) of events	116 (65)	46 (52)
Median OS, months	34.9	32.9
HR (95% CI)	1.07 (0.76–1.49)	
P value	0.714	

- BUT: Mortality in patients with ≥ 3 lines of prior chemotherapy: 70.0% olaparib vs 54.8% chemotherapy

Mirza M, IJGC, ESGO 2023 Abstr 161;
Penson R, Gynecol Oncol, August 2022

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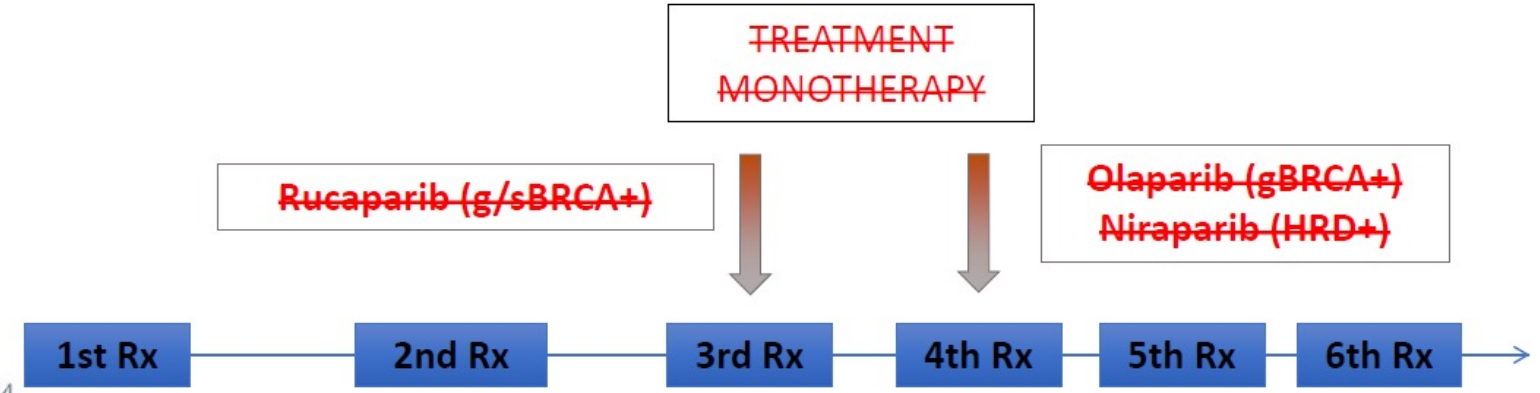
National Cancer Institute-Designated Comprehensive Cancer Center

Monotherapy for Recurrent Ovarian Cancer

- 12/2014 – ~~olaparib – gBRCA+ ROC~~ → 8/2022 withdrawal
- 12/2016 – ~~rucaparib – g/sBRCA+ ROC~~ → 6/2022 withdrawal
- 10/2019 – ~~niraparib – HRD+ ROC~~ → 9/2022 withdrawal



SGO 2024 WINTER MEETING

Society of Gynecologic Oncology

WHAT'S NEXT IN PARPI THERAPY?

Enhancement therapy

- Chemotherapy (DNA-damaging agents)
- Immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1)
- Radiation therapy

Resistance therapy

- P53 targeted agents (WEE-1, COTI-2, selinexor)
- CDK inhibitors (ribociclib, palbociclib, roniciclib)
- HDAC
- HSP90
- MEK

Contextual synthetic lethality (inducing HRD in HR proficient tumors)

- Hypoxia inducement (anti-angiogenesis, EZH2)
- PI3K pathway inhibitors
- ATR/ATM, CDK inhibitors, CHK1/2, pro-apoptotic agents (senolytic)

SUMMARY OF PARP

Niraparib: First-line maintenance treatment for advanced or recurrent ovarian cancer with complete or partial response to first-line platinum-based chemotherapy

Rucaparib: Maintenance therapy in platinum sensitive recurrent patients

Olaparib:

1. First-line maintenance treatment of BRCA mutated advanced ovarian cancer
2. First-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab
3. Maintenance therapy in platinum sensitive recurrent patients with BRCA mutations