Poly (ADP Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: Understanding the ASCO Guideline Rapid Recommendation Update

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November 11, 2022

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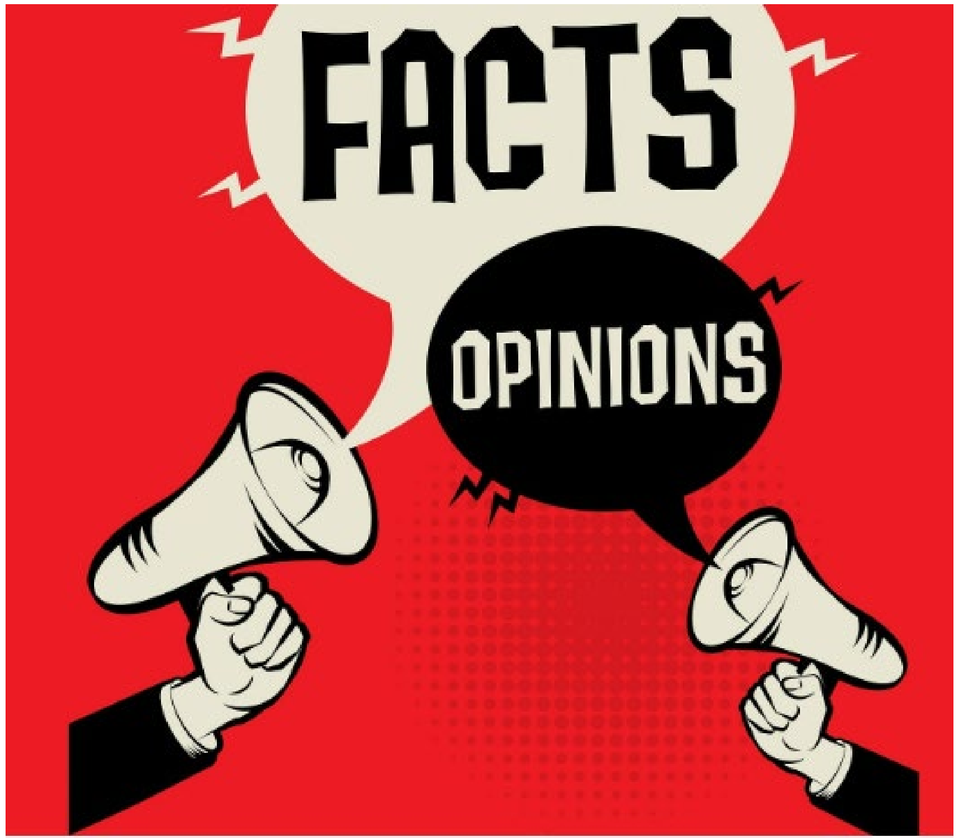
Disclosure:

I am on the expert panel for the ASCO PARPI Management Guidelines, however, this presentation is my own opinions and not representing the ASCO panel



Development and Evolution of the ASCO Practice Guidelines for Use of PARPi in the Management of Ovarian cancer: 2020 Version

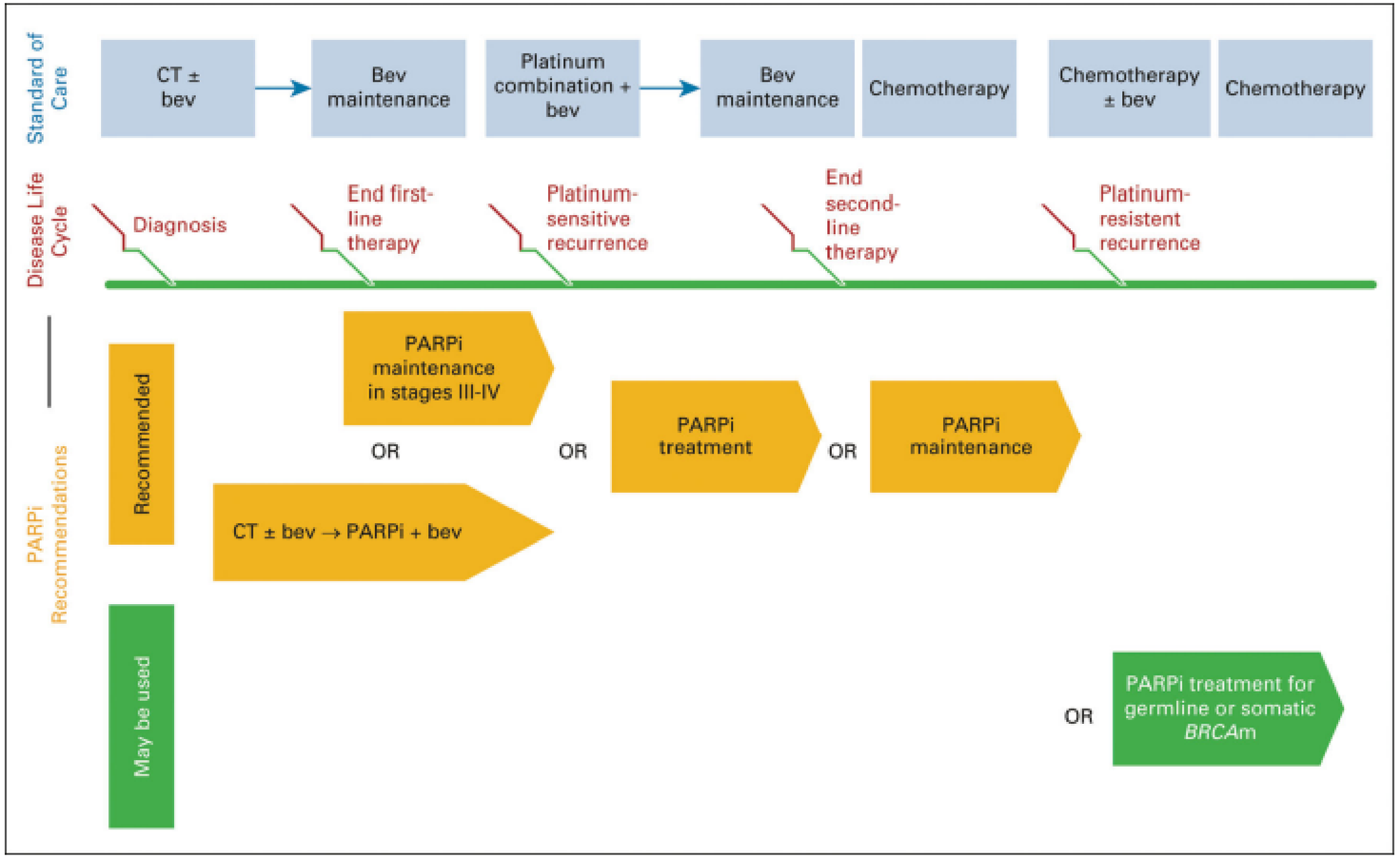
2020

PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline

William P. Tew, MD[1]; Christina Lacchetti, MHSc[2]; Annie Ellis[3,4]; Kathleen Maxian, BSW[5]; Susana Banerjee, PhD[6]; Michael Bookman, MD[7]; Monica Brown Jones, MD[8]; Jung-Min Lee, MD[9]; Stéphanie Lheureux, MD, PhD[10]; Joyce F. Liu, MD[11]; Kathleen N. Moore, MD[12]; Carolyn Muller, MD[13]; Patricia Rodriguez, MD[14]; Christine Walsh, MD[15]; Shannon N. Westin, MD[16]; and Elise C. Kohn, MD[9]

- Panel of 16 experts including patient advocate, academic, community physicians
- Evaluated 17 published, eligible trials to develop clinical practice guideline recommendations based on systematic review
- 5 Guideline Questions
  - Should PARPi be repeated
  - In which pts should PARPi be used in FL?
  - Is PARPi monotherapy recommended in recurrence
  - Are there settings for PARPi combinations
  - How should toxicities be managed?

2020-2022



Tew WP, Lacchetti C, Ellis A, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline. J Clin Oncol 38:3468-3493, 2020

Development and Evolution of the ASCO Practice Guidelines for Use of PARPi in the Management of Ovarian cancer: 2020 to Present

2020

PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline

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2020-2022

New Data on FL Ovarian Cancer Prompted Rapid Revision to the Guidelines

- Athena Mono
  - Monk BJ, et al: J Clin Oncol epub ahead of print on June 6, 2022

FDA Label Changes and Dear HCP Letters for NOVA, A3, SOLO3 and Quadra Occurred During Revision

- OS read out for NOVA
  - Matulonis et al. SGO 2021; Gynecol Oncol Volume 162, Supplement 1, August 2021, Pages S24-S25
- OS read out for SOLO3
  - Penson et al. SGO 2022: Gynecol Oncol Volume 166, Supplement 1, August 2022, Pages S19-S20
- OS read out for ARIEL4
  - Oza AM, et al: Presented at ESMO 2022, (abstr 5180)

2022

Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: ASCO Guideline Rapid Recommendation Update

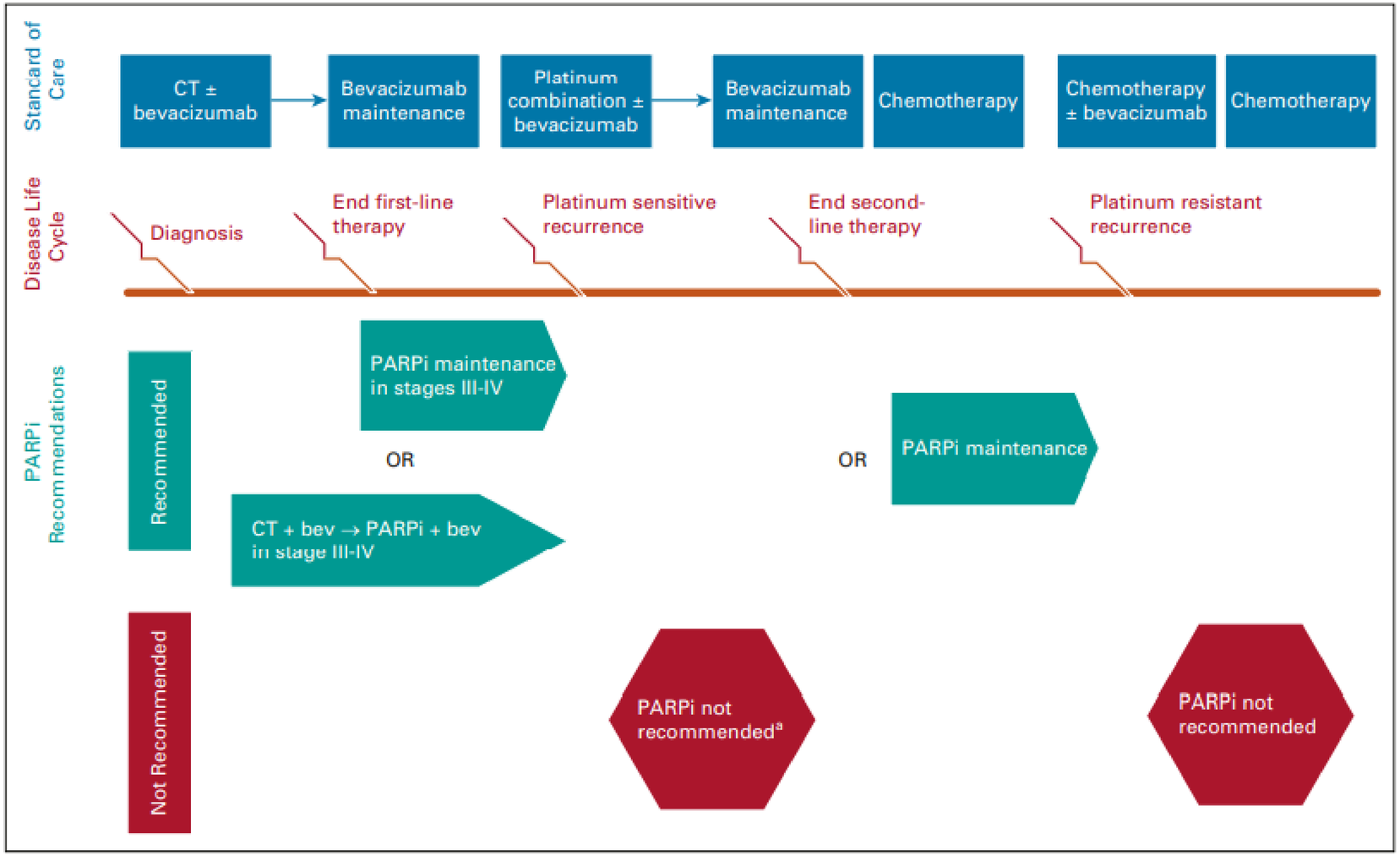
William P. Tew, MD[1]; Christina Lacchetti, MHSc[2]; and Elise C. Kohn, MD[3]; for the PARP Inhibitors in the Management of Ovarian Cancer Guideline Expert Panel

Given recent developments, the ASCO expert panel was reconvened virtually to provide a rapid update to the 2020 practice statement

- Update called to add Rucaparib to FL and then….
- Focused on revised recommendation strength for use of niraparib *maintenance* in PSOC and
- PARPi *treatment* in PSOC/PROC

Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022: DOI https://doi. org/10.1200/JCO.22. 01934

Development and Evolution of the ASCO Practice Guidelines for Use of PARPi in the Management of Ovarian cancer: Present Recommendations 2022



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Development and Evolution of the ASCO Practice Guidelines for Use of PARPi in the Management of Ovarian cancer: Present Recommendations 2022

Recommendation 2.2

The addition of olaparib to bevacizumab maintenance may be offered to patients who have stage III-IV, HGSOC or HGEOC and *BRCA*1 or *BRCA*2 genes and/or **genomic instability**, as determined by Myriad myChoice CDx, (Type: evidence based, benefits outweigh harms; Evidence quality: strong; Strength of recommendation: strong).

PARPi	First remission: maintenance	Second or greater remission: maintenance[b]
Olaparib	g/s*BRCA*	g/s*BRCA*
Olaparib combined with bevacizumab	g/s*BRCA*[a]	No
Niraparib	g/s*BRCA*; HRD; wt	g/s*BRCA*; HRD; wt
Rucaparib	g/s*BRCA*; HRD; wt	g/s*BRCA*; HRD; wt

Abbreviations. g/s*BRCA*, germline or somatic *BRCA*1/2 mutation; HRD, homologous recombination deficiency; wt, *BRCA*1/2 wild-type.

ASCO recommendations for PARPi use: should (**blue**), may (**red**), caution (**green**).

Edited notes:

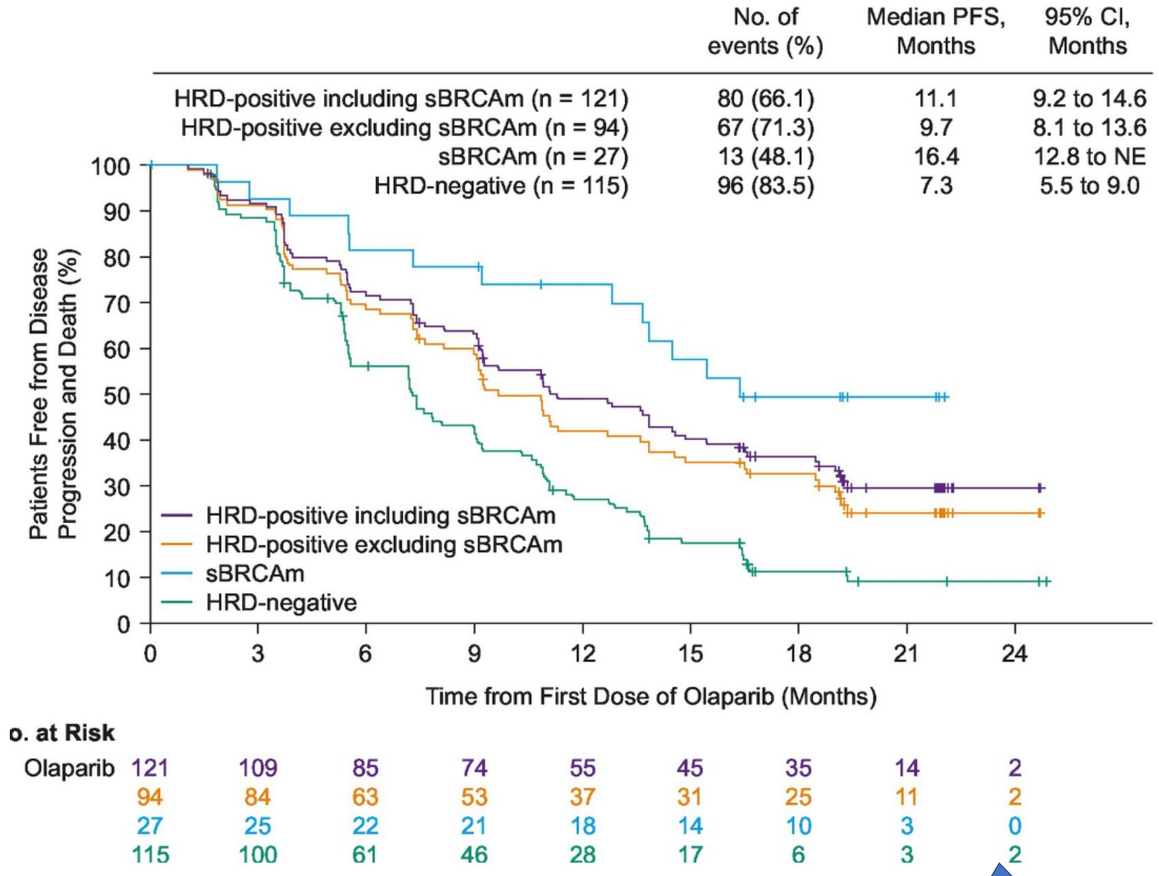
(1) PARPis are not recommended for use in combination with chemotherapy, nor is it recommended for monotherapy treatment.

(2) HRD score companion diagnostic (Myriad MyChoice for niraparib; FoundationOne CDx for rucaparib).

(3) Olaparib has not been studied in the HRD population. Olaparib may be considered an option in the HRD population in settings where any PARPi is recommended.

Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022: DOI https://doi.org/10.1200/JCO.22. 01934

Development and Evolution of the ASCO Practice Guidelines for Use of PARPi in the Management of Ovarian cancer: Present Recommendations 2022



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Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022: DOI https://doi.org/10.1200/JCO.22. 01934; Poveda et al. LIGHT Study – Gynecologic Oncology Volume 164, Issue 3, March 2022, Pages 498-504

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PARP INHIBITORS IN THE MANAGEMENT OF OVARIAN CANCER

RAPID RECOMMENDATION UPDATE AT-A-GLANCE SUMMARY

PARPi	First remission: maintenance	Second or greater remission: maintenance *(Indications for patients with no prior PARPi)*
Olaparib	**g/sBRCA**	**g/sBRCA; HRD**
Olaparib combined with bevacizumab	**g/sBRCA*; HRD**	No
Niraparib	**g/sBRCA; HRD; wt**	**g/sBRCA; HRD; wt**
Rucaparib	**g/sBRCA; HRD; wt**	**g/sBRCA; HRD; wt**

Color Key: should; may; caution.

Notes. *After completion of upfront chemotherapy, continue bevacizumab (1 year) and olaparib (2 years).

1. PARPis are not recommended for use in combination with chemotherapy, nor is it recommended for monotherapy treatment.
2. HRD score companion diagnostic (Myriad MyChoice for niraparib and olaparib; FoundationOne CDx for rucaparib).

asco.org/gynecologic-cancer-guidelines

Abbreviations. g/s *BRCA*, germline or somatic *BRCA*1/2 mutation; HRD, homologous recombination deficiency; PARPi, poly(ADP-ribose) polymerase inhibitor; wt, *BRCA*1/2 wild-type

The 2022 Practice Guideline Update Reinforce the Benefit of 1L PARPi maintenance

Patients with newly diagnosed stage III-IV HGSOC or HGEOC who are in complete or partial response to platinum-based chemotherapy should be offered PARPi maintenance. For those with BRCA1 or BRCA2 genes, options should include **olaparib** (2 years), **niraparib** (3 years) or **rucaparib** (2 years). For those who are HRD positive or negative, determined using FDA-approved companion diagnostic tests, **rucaparib** and **niraparib** are options. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of rec: Strong.)

	SOLO-1[1]	PAOLA-1[2]	PRIMA[3]	ATHENA- MONO[4]
Population	BRCAm	All comers	All comers	All comers
PARPi	Olaparib	Olaparib	Niraparib	Rucaparib
Bevacizumab	No	Yes	No	No
Comparator	Placebo	Placebo+ Bevacizumab	Placebo	Placebo
PFS	✓	✓	✓	✓

1. Banerjee S et al. Lancet Oncol. 2021;12:1721-1731. 2. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–2428 3. Gonzalez-Martin A, et al. 530P Presented at: ESMO Congress 9-13 September 2022; Paris, France. 4. Monk BJ, et al. Int J Gynecol Cancer 2021;31:1589–1594: Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022: DOI https://doi. org/10.1200/JCO.22. 01934

The 2022 Practice Guideline Update Reinforce the Benefit of 1L PARPi maintenance: This will likely remain given early signals of OS benefit

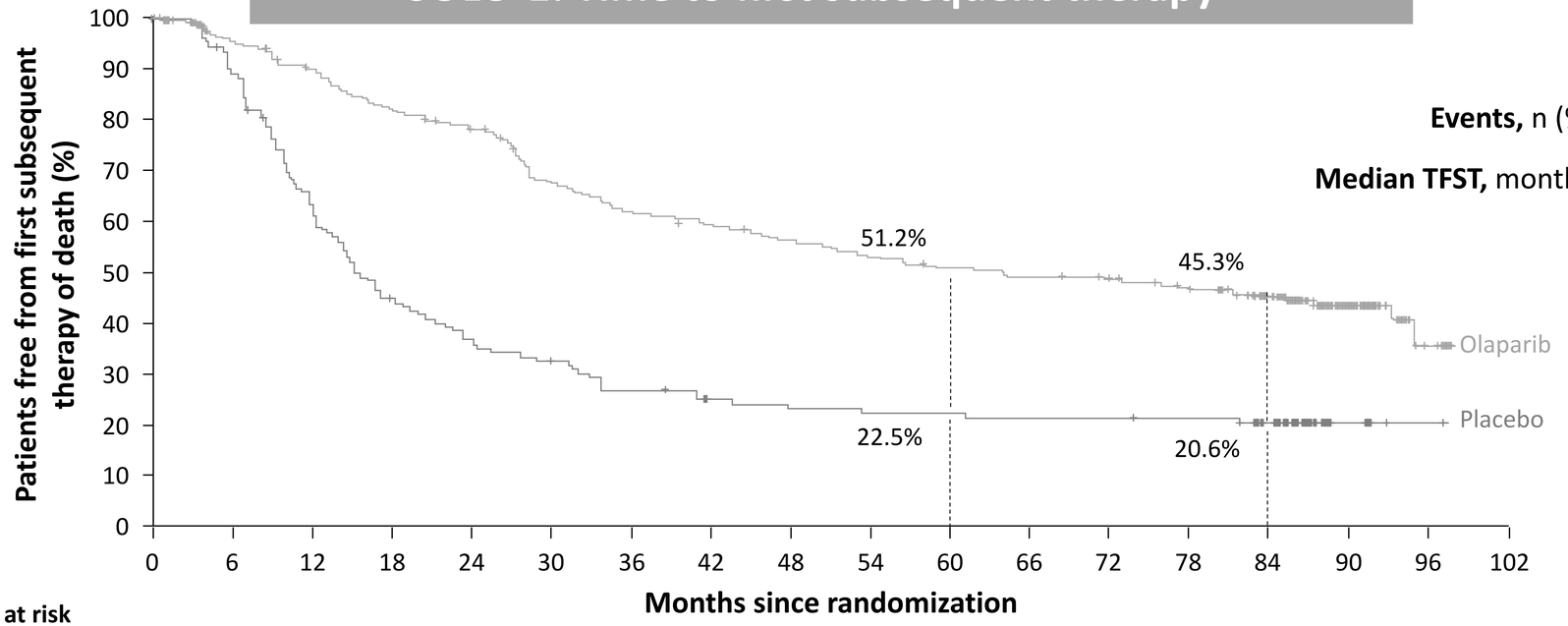
	SOLO-1[1]	PAOLA-1[2]	PRIMA[3]	ATHENA- MONO[4]
Population	BRCAm	All comers	All comers	All comers
PARPi	Olaparib	Olaparib	Niraparib	Rucaparib
Bevacizumab	No	Yes	No	No
Comparator	Placebo	Placebo+ Bevacizumab	Placebo	Placebo
PFS	✓	✓	✓	✓
OS	Presented at ESMO 2022[5,6]		–	–

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. Banerjee S et al. Lancet Oncol. 2021;12:1721-1731. 2. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–2428 3. Gonzalez-Martin A, et al. 530P Presented at: ESMO Congress 9-13 September 2022; Paris, France. 4. Monk BJ, et al. Int J Gynecol Cancer 2021;31:1589–1594 5. DiSilvestro P, et al. 517O Presented at: ESMO Congress 9-13 September 2022; Paris, France 6. Ray-Coquard I, et al. LBA29 Presented at: ESMO Congress 9-13 September 2022; Paris, France

Are we now beginning to see the possibility of cure for patients with advanced ovarian cancer and a BRCA mutation?

SOLO-1: Time to first subsequent therapy[1,2]



No. at risk

Olaparib	260	240	223	203	190	160	147	141	132	125	119	115	111	102	75	31	5	0
Placebo	131	114	79	55	45	39	32	28	26	25	25	24	24	23	18	4	1	0

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	**64.0**	**15.1**
HR 0.37 (95% CI 0.28–0.48)		

In the olaparib arm **45%** of patients who were still alive at 7 years had yet to receive any subsequent treatment

1. DiSilvestro P et al. J Clin Oncol 2022. 2. Di Silvestro.P, et al. 2022 J Clin Oncol.

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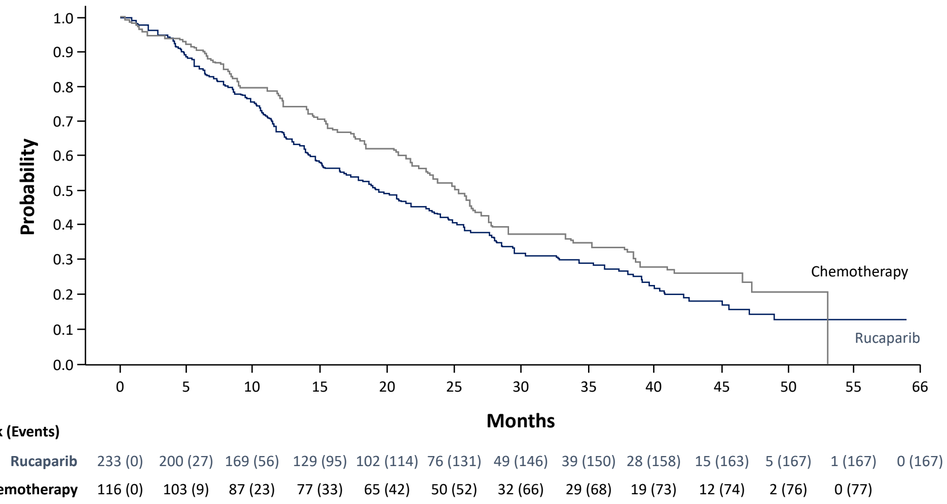
2022 Guidelines Caution Use of PARPi as *Treatment* in BRCA+ Recurrent Disease: Why?

PARPi monotherapy should not be routinely offered to patients for the **treatment** of recurrent platinum sensitive EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate.) Evidence on PARPi use in this setting is evolving. Any decision to proceed with PARPi treatment in select populations (BRCA +, PARPi naive, PSOC) should be individualized

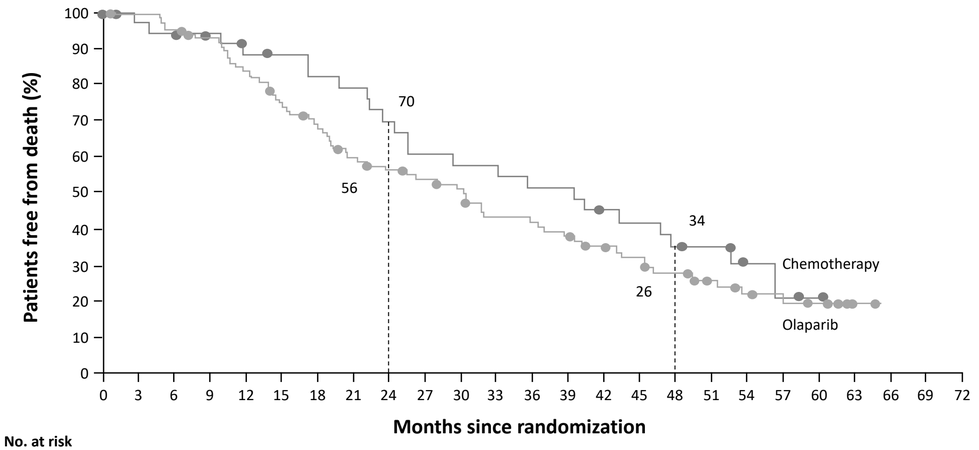
ARIEL4[1] (ITT population)



At Risk (Events)												
Rucaparib	233 (0)	200 (27)	169 (56)	129 (95)	102 (114)	76 (131)	49 (146)	39 (150)	28 (158)	15 (163)	5 (167)	1 (167)	0 (167)
Chemotherapy	116 (0)	103 (9)	87 (23)	77 (33)	65 (42)	50 (52)	32 (66)	29 (68)	19 (73)	12 (74)	2 (76)	0 (77)	

	ARIEL4[1]	
Median OS, months	Rucaparib **19.4**	Chemotherapy **25.4**
	HR 1.31 (95% CI 1.00–1.73)	

SOLO-3[2] (BRCAm PSR, ≥3 prior lines)



No. at risk																									
Olaparib	90	89	85	81	71	63	56	47	44	41	37	31	30	27	23	20	16	12	9	7	6	2	0	0	0
Chemotherapy	42	35	33	32	29	28	26	25	22	19	18	17	16	16	13	12	10	8	3	2	1	0	0	0	0

	SOLO-3[2]	
Median OS, months	Olaparib **29.9**	Chemotherapy **39.4**
	HR 1.33 (95% CI 0.84–2.18)	

1. Clovis Dear Health Care Provider Letter (Rucaparib), May 2022. 2.Leath C, et al. Presented at IGCS Annual Global Meeting, September 2022; Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022: DOI https://doi. org/10.1200/JCO.22. 01934

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DHCP Letter for Rucaparib in *BRCA*-Mutated Ovarian Cancer After ≥2 Chemotherapies - EMA

Direct Healthcare Professional Communication

Rucaparib (Rubraca®▼): interim data from Study CO-338-043 (ARIEL4) show a decrease in overall survival compared to standard of care

May 2022

Dear Healthcare Professional,

Clovis Oncology Ireland Ltd, in agreement with the European Medicines Agency (EMA) and the <National Competent Authority> would like to inform you of the following:

However, an OS detriment was observed at the planned IA with 51% data maturity (final OS analysis planned at 70%) with a median OS of 19.6 months in the rucaparib group compared to 27.1 months in the chemotherapy group resulting in an OS HR of 1.550 (95% CI: 1.085, 2.214), p=0.0161. Patients included in the study were stratified at the time of randomization according to platinum sensitivity (platinum sensitive vs. partially platinum sensitive vs. platinum resistant). The HRs for OS in that subgroups were 1.12 (95% CI: 0.44-2.88), 1.15 (95% CI: 0.62-2.11) and 1.72 (95% CI: 1.13-2.64), respectively. Final OS data from the ARIEL4 study are not yet available.

DHCP Letter for Rucaparib in *BRCA*-Mutated Ovarian Cancer After ≥2 Chemotherapies – US FDA

Dear Health Care Provider,

This letter is to inform you about an important change to the Rubraca® (rucaparib) United States Prescribing Information (USPI) for the treatment of BRCA-mutated ovarian cancer after 2 or more chemotherapies and is an update to the Rubraca DHCP letter dated May 2022.

Indications

Clovis Oncology has voluntarily withdrawn Rubraca for the treatment of adult patients with a 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. Revisions to the Rubraca USPI resulting from this withdrawal became effective June 10, 2022.

This decision was made in consultation with the U.S. Food and Drug Administration (FDA) after a detrimental effect in terms of overall survival (OS) was observed for rucaparib compared to the chemotherapy-containing control arm in the randomized Study CO-338-043 (ARIEL4; NCT02855944), a Phase 3 trial requested by FDA to confirm the clinical benefit of Rubraca (rucaparib) administered as treatment for BRCA-mutated ovarian cancer.

June 2022

This change does NOT impact the indication of monotherapy rucaparib 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.

Prescriber Action

Physicians who are treating patients with rucaparib for BRCA-mutated ovarian cancer after two or more chemotherapies should share this information with those patients so that they can make an informed decision regarding their ongoing care.

Physicians should not initiate new treatment with rucaparib for adult patients with a 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.

Slide courtesy of R. Coleman, MD

DHCP Letter for Olaparib in *gBRCA*-Mutated Ovarian Cancer After ≥3 Chemotherapies: Updated HCP Letter

SOLO3 met its primary endpoint of ORR and the key secondary endpoint of progression-free survival (PFS). These data have been previously analyzed in 2018 and published (Penson et al)[2].

The final OS analysis subsequently occurred in 2021. In a recent OS subgroup analysis, a potential survival detriment was observed in the subgroup of patients treated with 3 or more prior lines of chemotherapy corresponding to the current scope of the indication for Lynparza.

Table 1. SOLO3 Final OS, 60.9% maturity (data cut-off 16 Apr 2021): OS for Full Analysis Set and OS subgroup analysis in patients who had received 3 or more prior lines of chemotherapy

	Full Analysis Set 2 or more prior lines of chemotherapy		**3 or more prior lines of chemotherapy (Indicated population)**	
	Olaparib 300 mg bd (N=178)	**Chemo (N=88)**	**Olaparib 300 mg bd (N=90)**	**Chemo (N=42)**
Deaths, n (%)	116 (65.2)	46 (52.3)	63 (70.0)	23 (54.8)
Median (months)	34.9	32.9	29.9	39.4
	OS HR = 1.07 95% CI = 0.76, 1.49		OS HR = 1.33 95% CI = 0.84, 2.18	

Full indication retracted

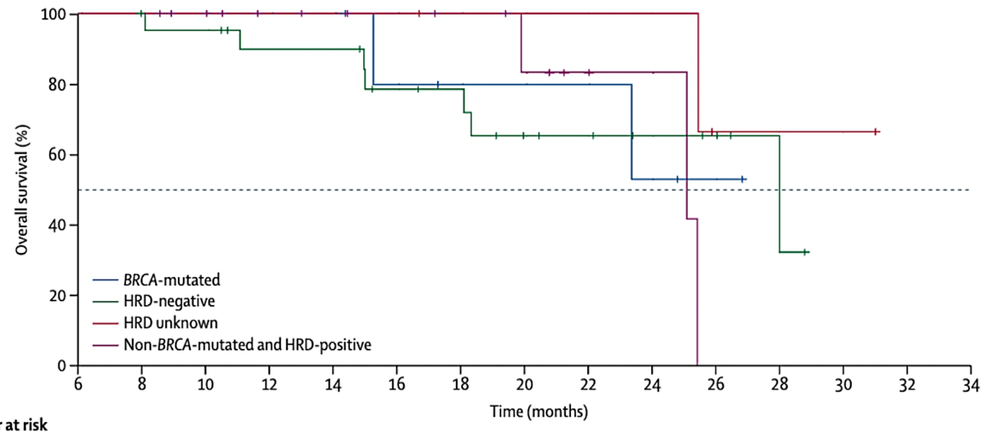
- AstraZeneca Letter to HCPs: IMPORTANT PRESCRIBING INFORMATION; Subject: Important Information for Lynparza (olaparib) for treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy is voluntarily withdrawn in the U.S. August 26, 2022.
2. Penson RT, et al. J Clin Oncol. 2020;38(11):1164-74.
- DHCP, healthcare provider.

Slide courtesy of R. Coleman, MD

QUADRA: Niraparib Improves Survival in *HRD*+ OC After ≥ 3 Chemotherapies

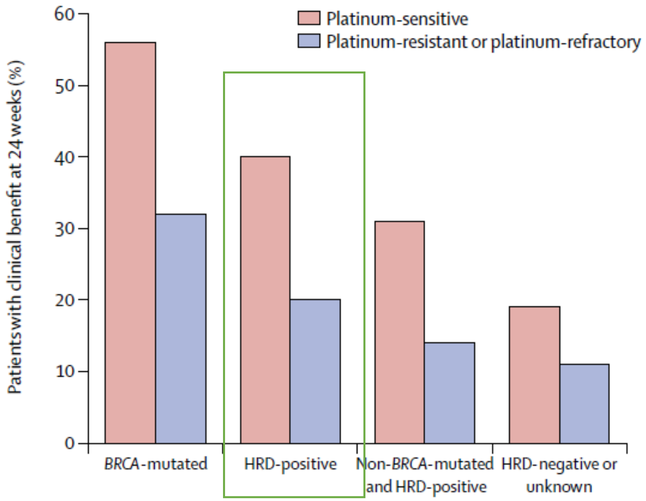
The study met the primary endpoint, with 13 (28%) of 47 pts who received 3 or 4 previous anticancer therapies with HRD+ tumors that were sensitive to the most recent Pt-based therapy and were PARPi naive (primary efficacy population) achieving an OR (95% CI, 15.6%–42.6%, one-sided *P*=0.00053); median duration of PFS was 5.5 months (95% CI, 3.5 months–8.2 months); mDOR=9.2 months (5.9 months–NE).

OS based on clinical benefit at 24 weeks



Number at risk (number censored)															
BRCA-mutated	6 (0)	6 (0)	6 (0)	6 (0)	6 (0)	4 (1)	3 (2)	3 (2)	3 (2)	2 (2)	1 (3)	0 (4)	..	..	..
HRD-negative	22 (0)	20 (1)	20 (1)	17 (3)	17 (3)	13 (5)	12 (6)	8 (8)	7 (9)	5 (11)	4 (12)	1 (14)	0 (15)	..	..
HRD unknown	4 (0)	4 (0)	4 (0)	4 (0)	4 (0)	4 (0)	3 (1)	3 (1)	3 (1)	3 (1)	1 (2)	1 (2)	1 (2)	0 (3)	..
Non-*BRCA*-mutated and HRD-positive	15 (0)	15 (0)	12 (3)	10 (5)	9 (6)	8 (7)	7 (8)	5 (9)	2 (12)	2 (12)	0 (12)	..	..	..	..

Clinical benefit at 24 weeks in subgroups defined by clinical (platinum status) and molecular biomarkers



Proportion of patients with a confirmed overall response by molecular biomarker and platinum status

	HRD-positive * (n=189)	BRCA-mutated (n=63)	HRD-negative or unknown (n=230)
Platinum-sensitive to most recent line of platinum therapy, n/N (%)	14/53 (26%)	7/18 (39%)	2/52 (4%)
Platinum-resistant or refractory, n/N (%)	12/120 (10%)	10/37 (27%)	5/169 (3%)
Platinum status unknown, n/N (%)	3/16 (19%)	1/8 (13%)	1/9 (11%)
All, n/N (%)	29/189 (15%)	18/63 (29%)	8/230 (3%)

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Moore KN, et al. *The Lancet.* 2019

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DHCP Letter for Niraparib in *HRD* Ovarian Cancer After ≥3 Chemotherapies

14 September 2022

IMPORTANT PRESCRIBING INFORMATION

Subject: ZEJULA® (niraparib) for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens is voluntarily withdrawn in the U.S.

Dear Health Care Provider,

This letter is to inform you about an important change to the ZEJULA (niraparib) United States Prescribing Information (USPI) for the **treatment** of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status. The letter is an update to the DHCP letter dated September 2022

Indications

GSK has voluntarily withdrawn the ZEJULA indication for the **treatment** of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status.

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Slide courtesy of R. Coleman, MD

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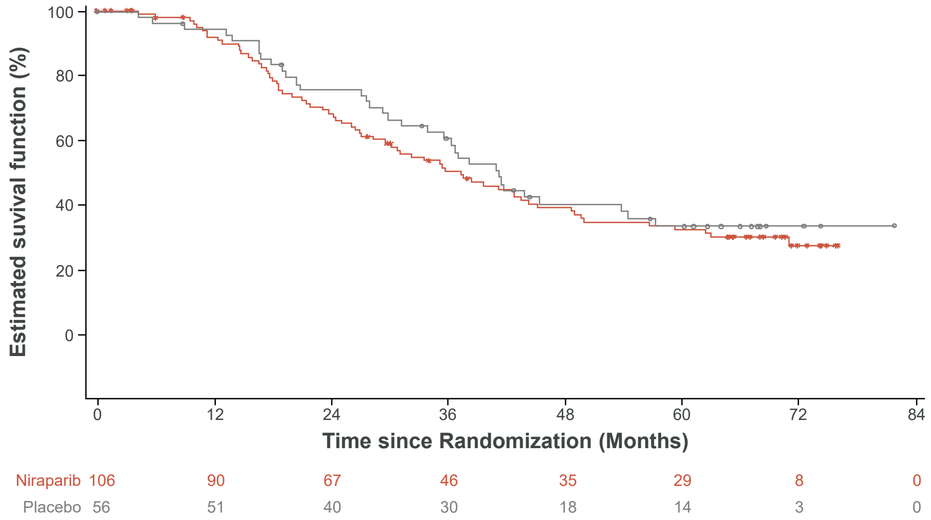
2022 Guidelines Caution Use of PARPi as *Maintenance* in BRCAwt/HRD PSOC: Why?

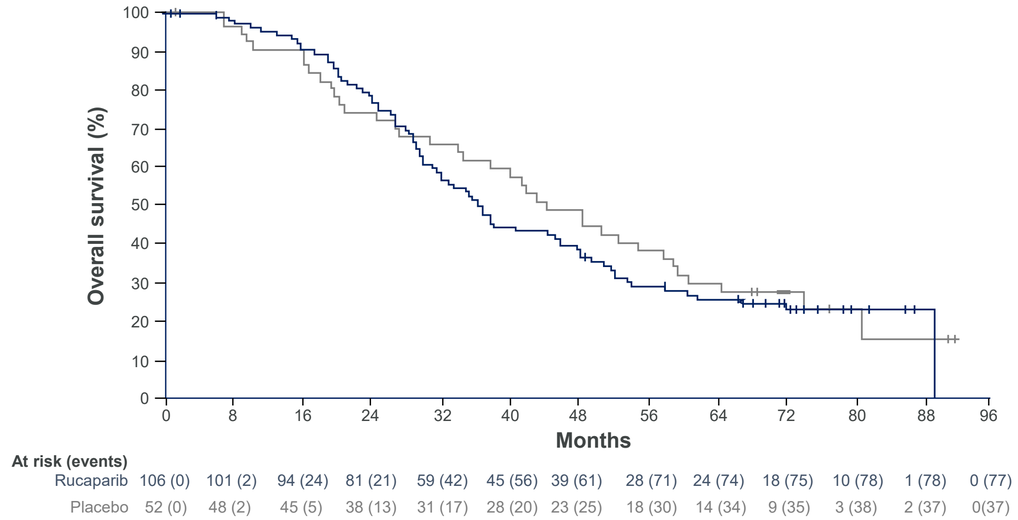
PARPi maintenance (second-line or more) may be offered to PARPI naïve patients who have responded to platinum-based therapy regardless of BRCA. Options include olaparib, rucaparib or niraparib. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.) **Maintenance treatment with niraparib for BRCAwt should weigh potential PFS benefit against possible OS decrement.** (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate.)

NOVA[1] (non-gBRCAm, HRD+ cohort)



	NOVA[1]	
Median OS, months	Niraparib **37.3**	Placebo **41.4**
	HR 1.32 (95% CI 0.84–2.06)	

ARIEL3[2] (BRCAwt, LOH-high cohort)



	ARIEL3[2]	
Median OS, months	Rucaparib **36.8**	Placebo **44.7**
	HR 1.280 (95% CI 0.841–1.948)	

1. GSK Dear Health Care Provider Letter (Niraparib), May 2022. 2. Coleman R presented at IGCS Annual Global Meeting, September 2022; Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022: DOI https://doi. org/10.1200/JCO.22. 01934

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DHCP Letter for Niraparib For Maintenance in PS-ROC After ≥2 Chemotherapies

May 2022

IMPORTANT DRUG WARNING

Subject: Zejula (Niraparib) Important Drug Warning For The Maintenance Treatment In Recurrent Ovarian Cancer (2L+)

Dear Health Care Provider:

The purpose of this letter is to inform you of important information for Zejula® (niraparib) a poly (ADP-ribose) polymerase (PARP) inhibitor indicated 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 2nd line or higher settings. GlaxoSmithKline (GSK) would like to inform you of updated overall survival (OS) data from the ENGOT- OV16/NOVA study.

Updated OS Data from the ENGOT-OV16/NOVA study, a Phase III trial which evaluated the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer

- The primary endpoint of the study was progression free survival, which demonstrated the benefit of niraparib in patients with g*BRCA*mut and non-g*BRCA*mut ovarian cancer, including the HRD subgroups of non-g*BRCA*mut cohort.
- The observed overall survival (OS) results based on the currently available data (data cutoff date of October 1, 2020) are included below:
  - In the g*BRCA*mut cohort (N=203), the median OS was 43.6 months for patients treated with niraparib compared to 41.6 months for patients on placebo (HR = 0.93 [95% CI 0.63, 1.36])
  - In the non-g*BRCA*mut cohort (N=350), the median OS was 31.1 months for patients treated with niraparib compared to 36.5 months for patients on placebo (HR = 1.10 [95% CI 0.83, 1.46])
  - In the non-g*BRCA*mut, HRDpos subgroup (n=162), the median OS was 37.3 months for patients treated with niraparib compared to 41.4 months for patients on placebo (HR = 1.32 [95% CI 0.84, 2.06]).

    The OS Kaplan Meier (KM) curves for the non-g*BRCA*mut cohort (Figure 1) and the non-g*BRCA*mut, HRDpos subgroup (Figure 2) are included below.

  - As of the October 1, 2020 data cutoff date, 14% of patients in both the g*BRCA*mut and non-g*BRCA*mut cohorts had missing OS data. GSK is taking action to capture additional OS data in an effort to decrease the amount of missing survival information and intend to provide FDA with an updated OS analysis upon completion of our efforts.
- The current OS results indicate a possible OS detriment to patients in the overall non-g*BRCA*mut cohort and to patients in the non-g*BRCA*mut/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.
- These data are under review by the FDA.

Pending

Oncologic Drugs Advisory Committee to review Zejula overall survival data from the NOVA phase III trial in recurrent ovarian cancer

Issued: London UK

For media and investors only

GSK plc (LSE/NYSE: GSK) today announced that the US Food and Drug Administration (FDA) will convene a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss overall survival (OS) data from the ENGOT-OV16/NOVA phase III clinical trial. NOVA is a randomised, double-blind, placebo-controlled phase III trial of *Zejula* (niraparib), an oral, once-daily poly (ADP-ribose) polymerase (PARP) inhibitor for the maintenance treatment of women with platinum-sensitive recurrent ovarian cancer.

The phase III NOVA trial met the primary endpoint of progression-free survival (PFS) in both the gBRCAm and non-gBRCAm cohorts, demonstrating a statistically significant and clinically meaningful treatment effect of *Zejula* in this patient population, regardless of biomarker status. These PFS results served as the primary basis for the US FDA approval for the maintenance treatment of women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Overall survival was a secondary endpoint. Updated final overall survival data was recently shared with the FDA.

Hesham Abdullah, SVP, Global Head of Oncology Development, GSK said: "We believe PARP inhibitors, including *Zejula*, are important options for the maintenance treatment of patients with recurrent ovarian cancer, across all biomarker subgroups, who are in complete or partial response to platinum-based chemotherapy. We look forward to continuing our ongoing discussions with the FDA."

The ODAC meeting is scheduled for 22 November 2022. This is not related to the niraparib indication in the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

About ovarian cancer

Ovarian cancer is the eighth most common cancer in women worldwide.[1] Despite high response rates to platinum-based chemotherapy in the front-line setting, approximately 85% of patients will experience disease recurrence.[2] Once the disease recurs, it is rarely curable, with decreasing time intervals to each subsequent recurrence.

About *Zejula* (niraparib)

Zejula is an oral, once-daily PARP inhibitor currently being evaluated in multiple pivotal trials. GSK is building a robust clinical development programme by assessing activity across multiple tumour types and evaluating several potential combinations of *Zejula* with other therapeutics. The ongoing development programme includes several combination studies.

ZEJULA is indicated:

Dear HCP Letters: OS Efficacy Summary

<table>
<tr><th>SOLO3[1,a]
olaparib vs chemotherapy</th><th colspan="3">ARIEL3[2]
rucaparib vs placebo</th><th colspan="3">ARIEL4[3]
rucaparib vs physician's choice chemo</th><th colspan="2">NOVA[4]
niraparib vs placebo</th><th>QUADRA[5,6,b]
niraparib</th></tr>
<tr><td>All patients (gBRCAm)
n: 178 vs 88
mOS: 34.9 vs 32.9
HR: 1.07
95% CI: 0.76–1.49</td><td rowspan="2">ITT
n: 375 vs 189
mOS: 36 vs 43.2
HR: 0.995
95% CI: 0.809-1.223</td><td rowspan="2">BRCAm
n:130 vs 66
mOS: 45.9 vs
HR:0.832
95% CI: 0.581-1.192</td><td rowspan="2">HRD
n: 236 vs 118
mOS:40.5 vs 47.8
HR: 1.005
95% CI: 0.766-1.320</td><td>ITT
n: 233 vs 116
mOS:19.4 vs 25.4
HR: 1.313
95% CI: 0.999-1.725</td><td>Excluding Crossover
n: 233 vs 36
mOS: 19.4 vs 9.1
HR: 0.423
95% CI: 0.276-0.650</td><td>Censoring at Crossover
n: 233 vs 116
mOS:19.4 vs 26.2
HR: 1.059
95% CI: 0.688-1.630</td><td>non-gBRCAm
n: 234 vs 116
mOS: 31.1 vs 36.5
HR: 1.10
95% CI: 0.831-1.459</td><td>non-gBRCAm (IPCW analysis)
n: 234 vs 116
mOS: 31.3 vs 35.9
HR: 0.97
95% CI: 0.74-1.26</td><td rowspan="3">≥3L prior lines
HRD+
n: 98
mOS:23.3 months 95% CI: 17.2-28.0</td></tr>
<tr><td>gBRCAm
2L prior lines
n: 88 vs 46
mOS: 37.9 vs 28.8
HR: 0.83
95% CI: 0.51–1.38</td><td colspan="3">Plat-resistant
n: 120 vs 59
mOS:14.2 vs 22.2
HR:1.511
95% CI: 1.053 vs 2.170</td><td rowspan="2">gBRCAm
n:138 vs 65
mOS: 43.6 vs 41.6
HR:0.93
95% CI: 0.633-1.355</td><td rowspan="2">gBRCAm (IPCW analysis)
n:138 vs 65
mOS:43.8 vs 34.1
HR: 0.66
95% CI: 0.44-0.99</td></tr>
<tr><td>gBRCAm
≥3L prior lines
n: 90 vs 42
mOS: 29.9 vs 39.4
HR: 1.33
95% CI: 0.84–2.18</td><td>BRCAwt/LOH-High
n: 106 vs 52
mOS: 36.8 vs 44.7
HR: 1.280
95% CI: 0.841-1.948</td><td>BRCAwt/LOH-Low
n: 107 vs 54
mOS: 28.6 vs 32.6
HR: 1.153
95% CI: 0.784-1.695</td><td>BRCAwt/LOH-Unknown
n: 32 vs 17
mOS: 33.9 vs 26.7
HR: 0.673
95% CI: 0.305-1.483</td><td>Plat-sensitive
n: 113 vs 57
mOS: 29.4 vs 27.6
HR: 1.071
95% CI: 0.709-1.618</td><td>Partially Plat-sensitive
n: 65 vs 31
mOS: 21.1 vs 23.2
HR:0.972
95% CI: 0.583 vs 1.621</td><td>Fully Plat-sensitive
n: 48 vs 26
mOS: 36.3 vs 47.2
HR: 1.243
95% CI: 0.619-2.498</td></tr>
</table>

Leath III CA, et al. IGCS 2022. LB001.
Coleman et al. IGCS 2022. Abstract 376.
Oza et al. ESMO 2022. Abstract 518MO.
Matulonis UA et al. SGO 2021. Abstract 37.
Moore KN, et al. *The Lancet.* 2019.

[a]3 prior lines of therapy, HR 1.20 (0.66–2.29); ≥4 prior lines of chemotherapy HR=1.58, (0.77–3.69)
[b]HRD+ defined as BRCAmut regardless of platinum status and non-BRCAmut HRD+ platinum sensitive disease

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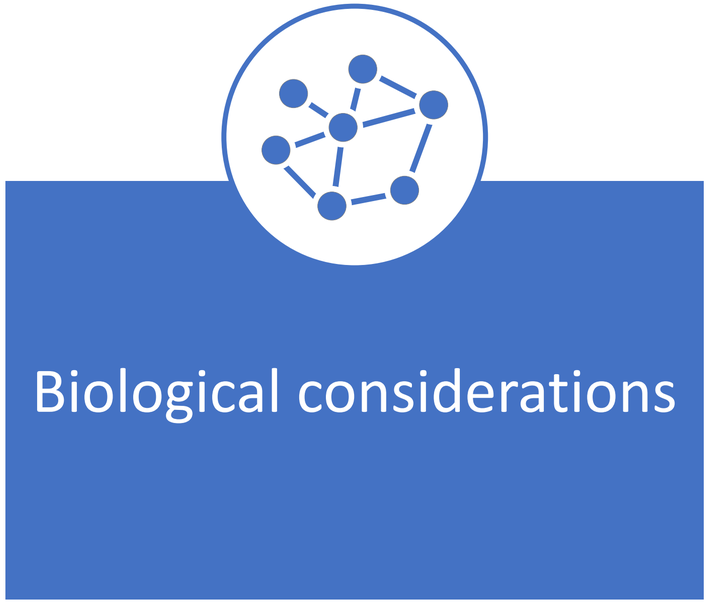
Slide courtesy of R. Coleman, MD

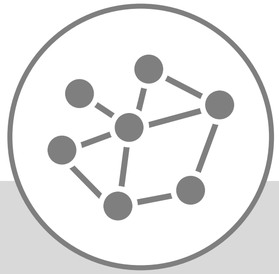
GOG Highlight Reel

There may be a variety of explanations for these data



There may be a variety of explanations for these data

Statistical considerations



Biological considerations

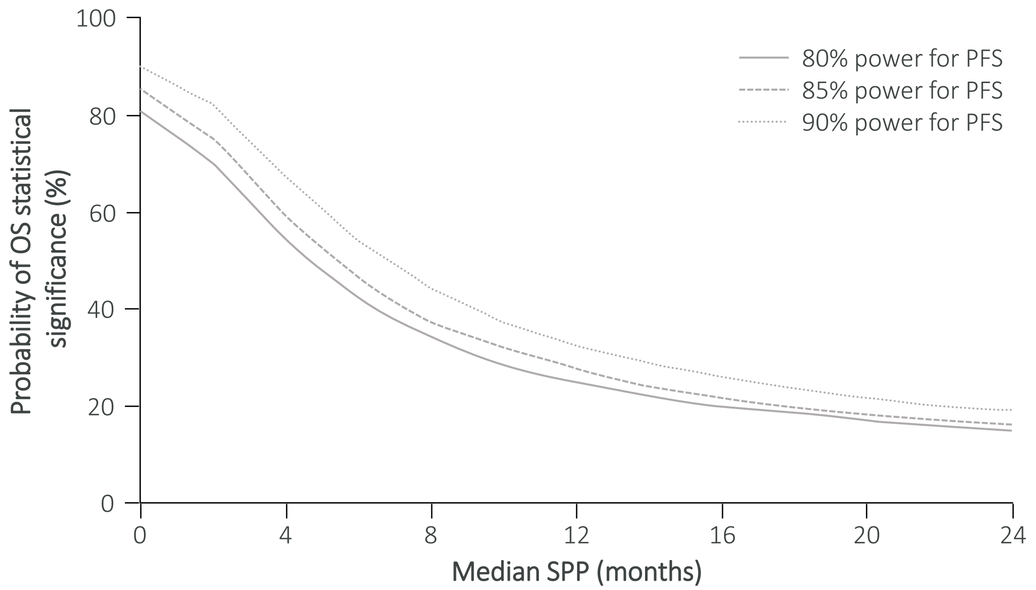
Crossover can confound analysis of OS

- Patients in ovarian cancer trials can often receive a variety of post-progression treatments and experience a long post-progression survival, making it difficult to demonstrate improvements in OS

- Crossover to a PARPi at progression in patients in the placebo arm of a trial raises the bar for observing any OS benefit from the experimental treatment

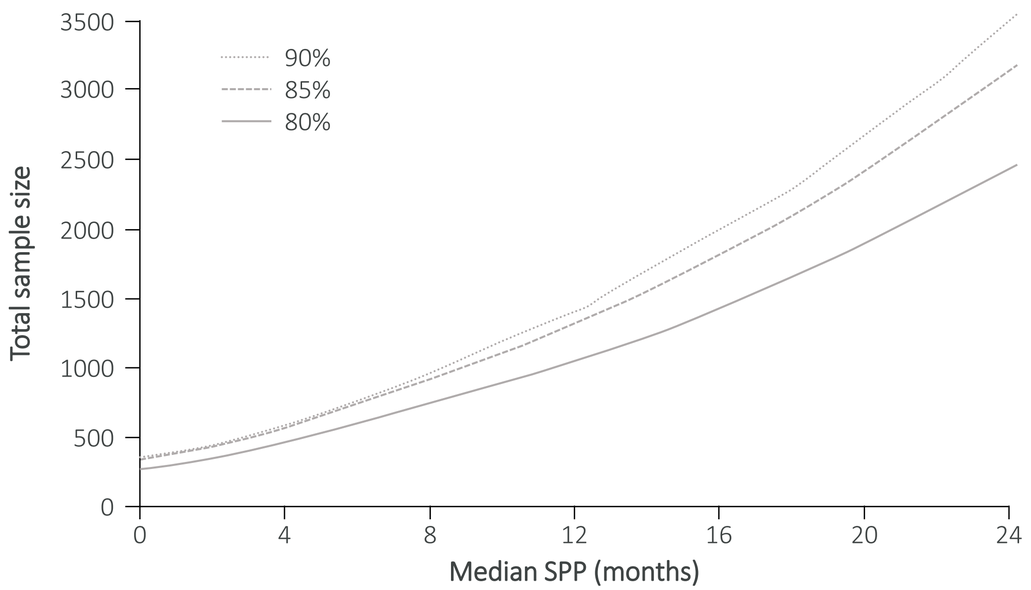
Long post-progression survival makes demonstrating an OS benefit challenging

Probability of statistically significant differences in OS as a function of median survival post-progression (SPP)



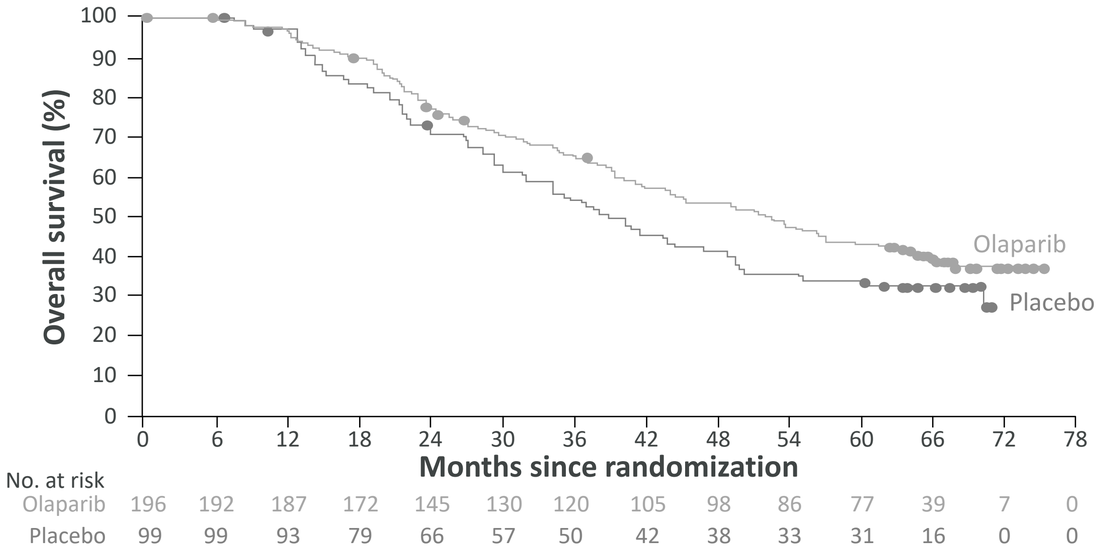
Long post-progression survival makes it harder to show a 3-month difference in OS from 6 to 9 months

Sample sizes required for detecting a statistically significant difference in OS by median survival post-progression (SPP)



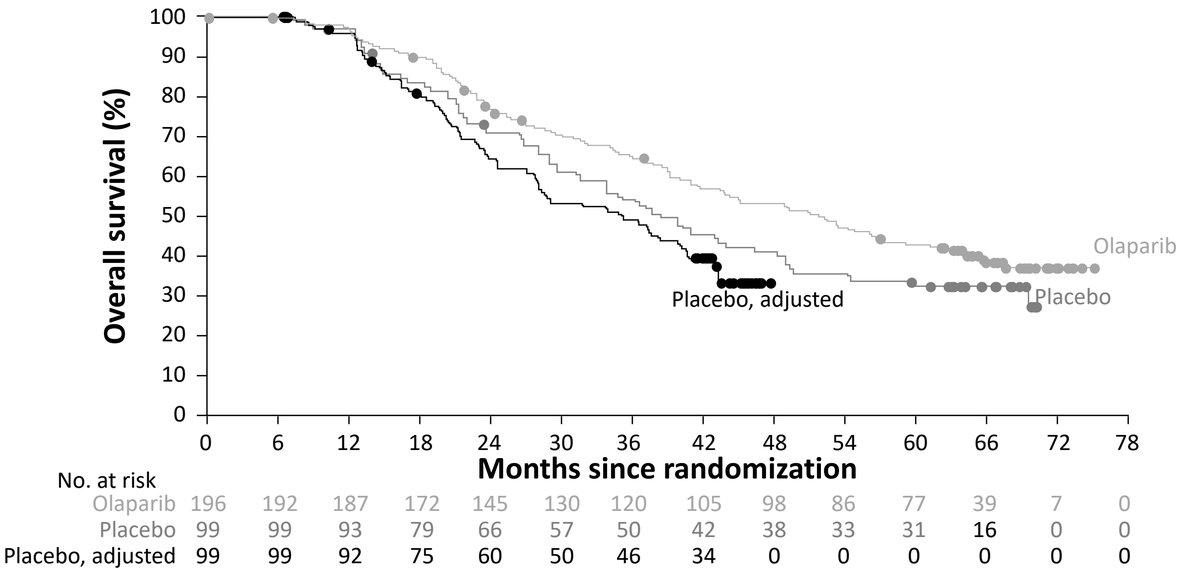
For long post-progression survival a very large sample size is needed to show a statistically different OS outcome

Adjusting for crossover in SOLO-2 revealed an OS benefit from maintenance olaparib in patients with gBRCAm PSR OC



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	**51.7**	**38.8**
	HR 0.74 (95% CI 0.54–1.00); *P*=0.0537	

38% of placebo patients and 10% of olaparib patients in SOLO-2 received subsequent PARPi therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [60% maturity]	116 (59)	61 (62)
Median OS, months	**51.7**	**35.4**
	HR 0.56 (95% CI 0.35–0.97)	

Excluding crossover shows benefit

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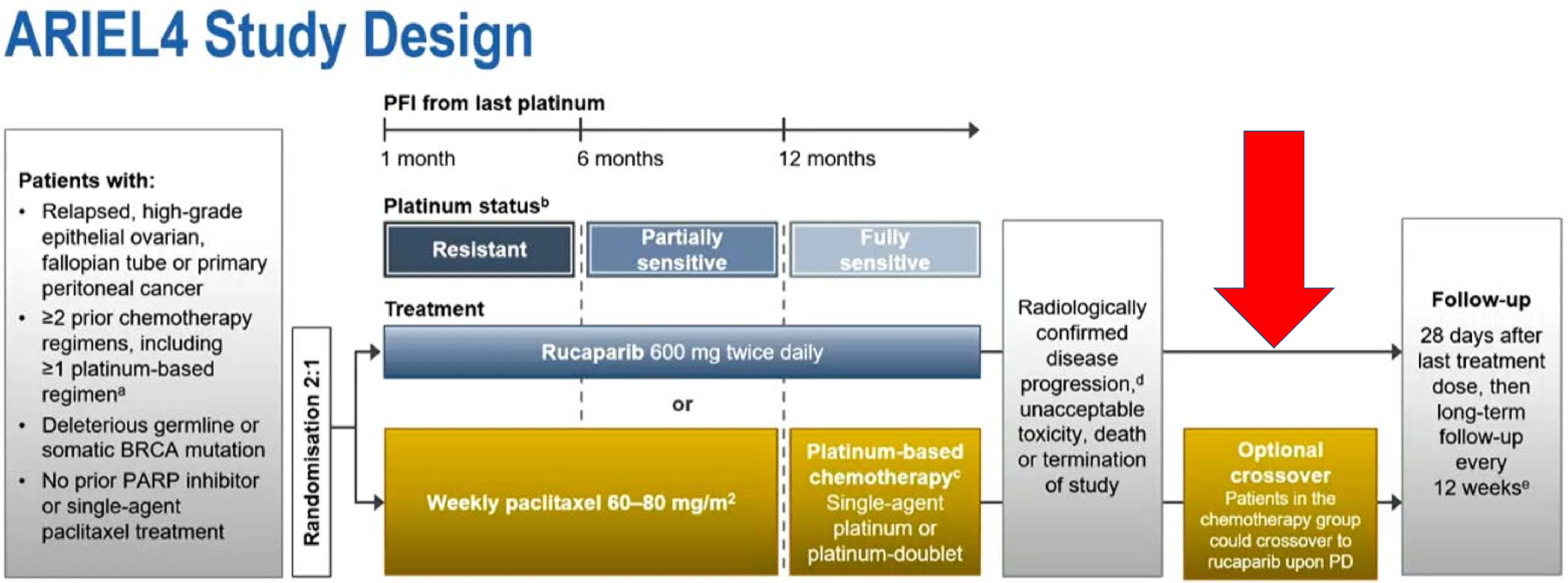
Poveda et al ASCO 2020; Lancet Oncol 2021

GOG Highlight Reel

ARIEL 4 provides an excellent example of the impact subsequent therapy and cross over can have……

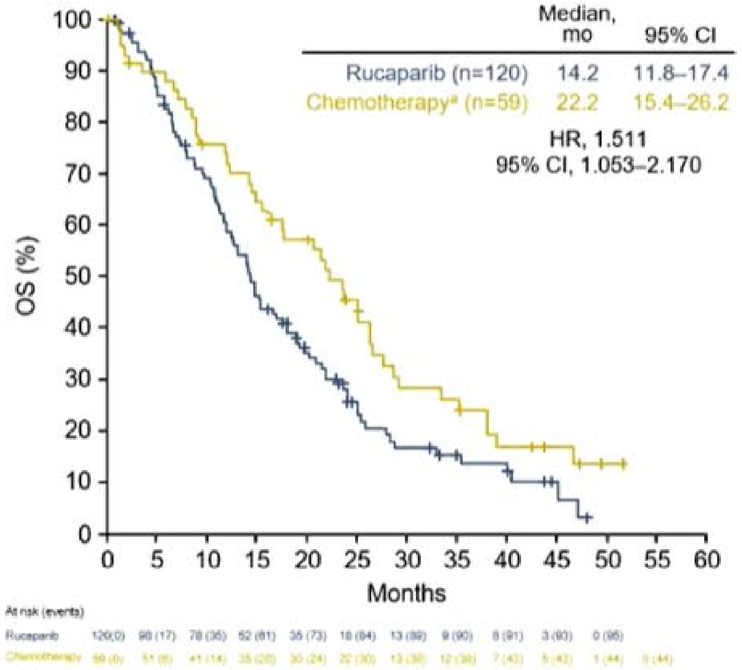


How do you interpret this in light of the fact that for the IIT group: 19% of patients randomized to chemotherapy received no further therapy as compared to 42% of patients randomized to rucaparib?

OS: Platinum Status Subgroups

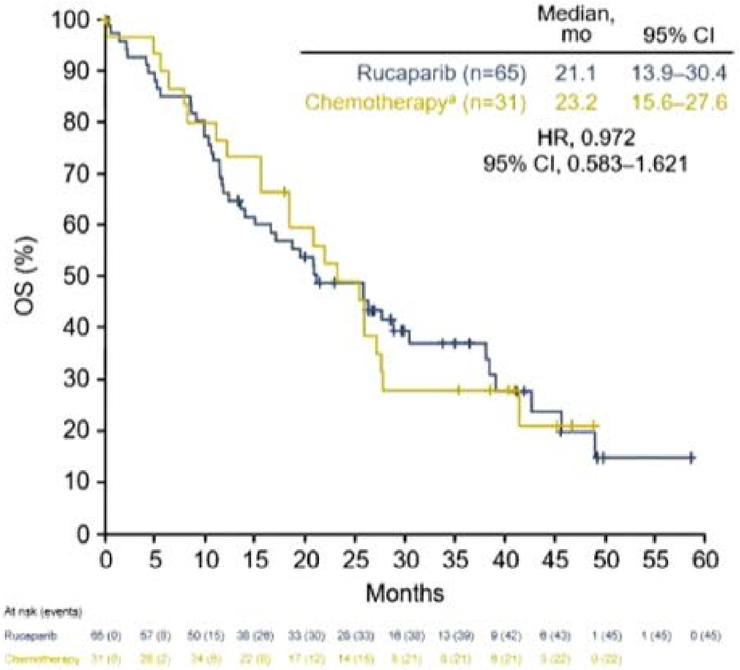
This is not interpretable data for OS

Platinum Resistant



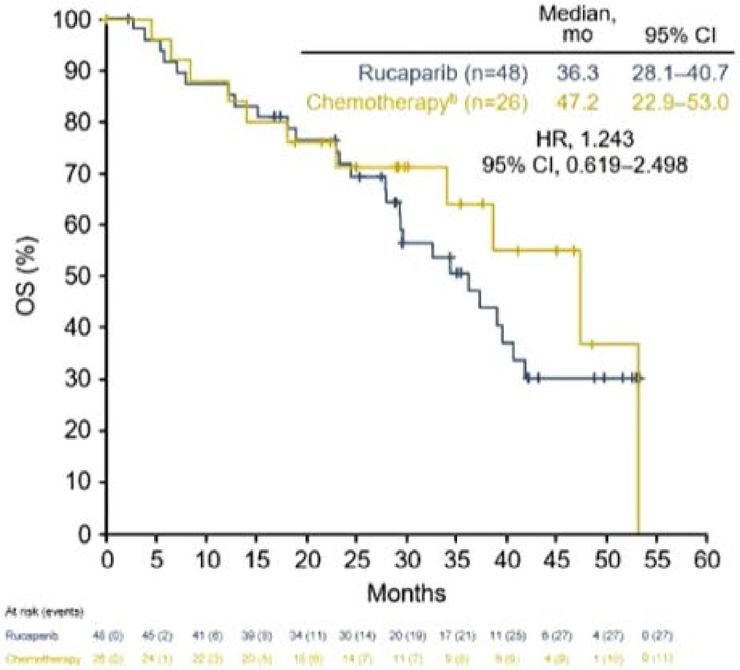
Rucaparib arm: 42.7% NFT
CT arm: 23.7% NFT
CT arm: 91% of FT = Rucaparib

Partially Platinum Sensitive



Rucaparib arm: 38.5% NFT
CT arm: 16.1% NFT
CT arm: 96% of FT = Rucaparib

Fully Platinum Sensitive



Rucaparib arm: 48.5% NFT
CT arm: 15.4% NFT
CT arm: 63% of FT = Rucaparib
Rucaparib arm: 76% of FT = plat

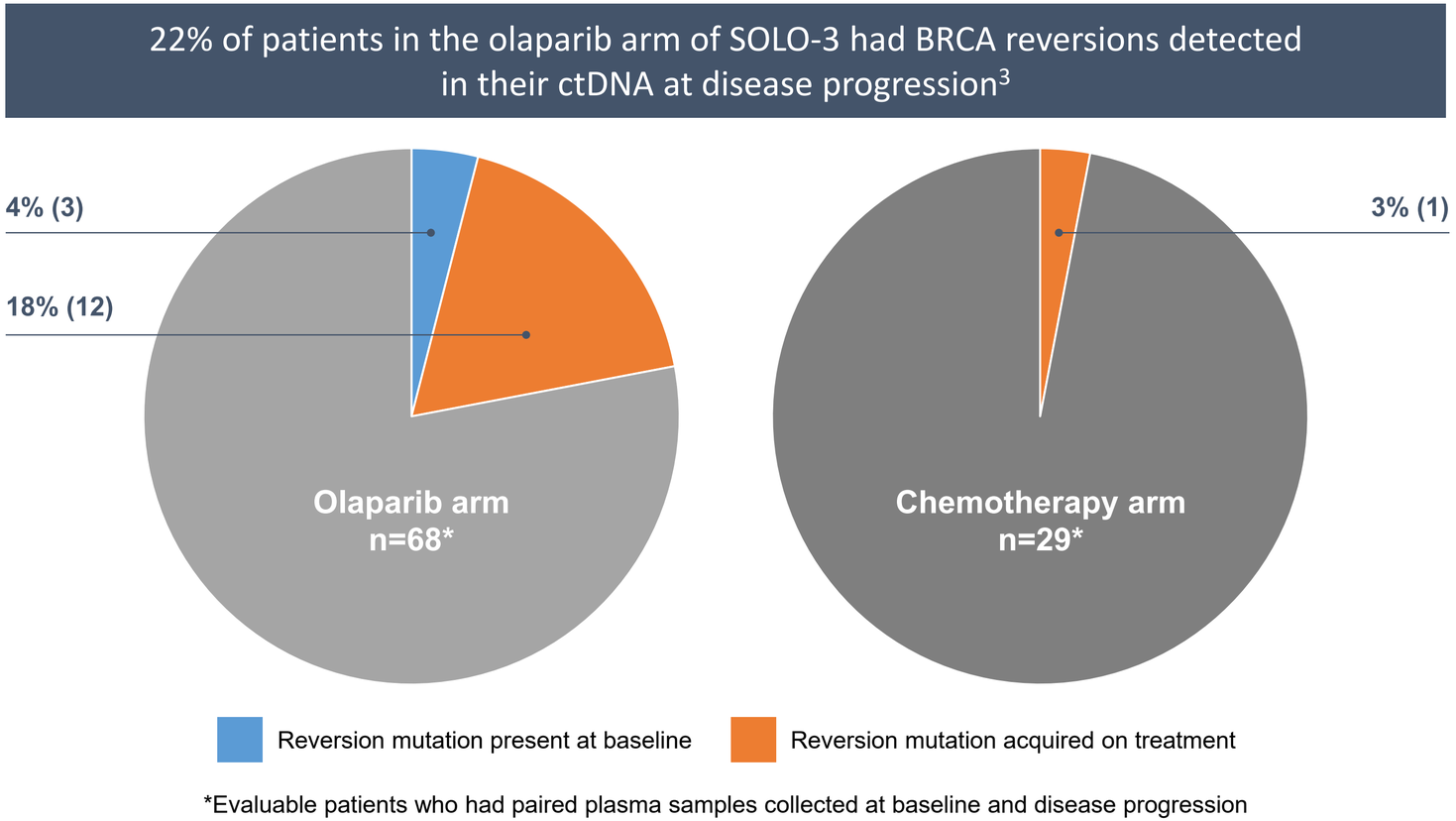
There may be a variety of explanations for these data

Statistical considerations

Biological considerations

Could BRCA reversions contribute to worse OS outcomes with PARPi vs chemotherapy in late line relapsed OC?

- BRCA reversions are a mechanism of resistance to PARPi inhibitors and platinum-based chemotherapy[1]
- In SOLO-3, no responses to olaparib were seen for patients with BRCA reversions identified at baseline[2]



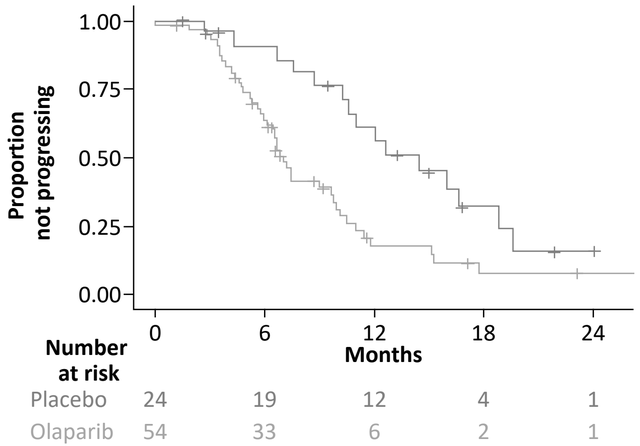
1. Leath CA, et al. IGCS Annual Global Meeting, September 29 to October 1, 2022. 2. Penson RT, et al. Society of Gynecologic Oncology 2022 Annual Meeting on Women's Cancer; 18–21 March 2022; abstract 26; 3. Lukashchuk N, et al. J Clin Oncol 2022; 40 (Suppl 16): abstr 5559 and poster presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2022; 3–7 June 2022; poster 438.

Does use of a PARPi in PSR OC have the potential to induce platinum resistance?

Post hoc analysis of SOLO2 / ENGOT Ov-21

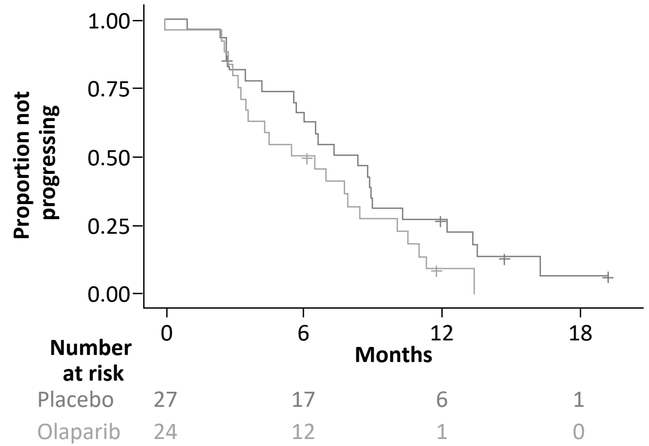
- Assessed the efficacy of chemotherapy at first disease progression, based on time between first progression and second progression or death (i.e., PFS2 minus PFS)
- Reduced efficacy of subsequent platinum was observed in patients who had received olaparib maintenance vs placebo

Patients retreated with platinum* (n=78)



	Olaparib	Placebo
Median, months	**7.0**	**14.6**
	HR 2.33 (95% CI 1.27–4.28)	

Patients retreated with non-platinum-based regimens (n=51)



	Olaparib	Placebo
Median, months	**6.0**	**8.3**
	HR 1.58 (95% CI 0.86–2.90)	

Caveat: analysis based on small numbers of patients selected for progression on PARPi

*Excluding those in the placebo arm who had received PARPI maintenance after platinum

Frenel JS et al. Ann Oncol 2022 Oct;33(10):1021-1028.

We should remain circumspect about recent OS data from trials investigating PARPi as maintenance or treatment in relapsed OC

- Recent OS data from SOLO-1 and PAOLA-1 indicate that 1L olaparib maintenance may enhance the potential for cure in some patients
  - HRD testing is essential to predict the likely magnitude of benefit from 1L PARPi maintenance in individual patients

- For some patients, maintenance after relapse may be the first opportunity to receive a PARPi
  - There was a survival difference between PARPi maintenance and placebo in SOLO-2, although not statistically significant
- PARPi maintenance for BRCAwt patients with relapsed OC
  - We need to consider carefully how to interpret the OS data from NOVA and ARIEL3

- PARPi as late-line treatment for patients with relapsed OC
  - Recent data have led to the withdrawal of late-line treatment indications for rucaparib, olaparib and niraparib (ARIEL4, SOLO-3 and QUADRA)