PARP inhibitors in ovarian cancer: Clinical updates from SGO 2023

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Recorded following the SGO Annual Meeting on Women's Cancer 2023, 25–28 March

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Agenda

Update on first-line PARPi maintenance in ovarian cancer: Where are we now?

Selection and sequencing implications for PARPis in ovarian cancer emerging from the latest data: What should we consider, and when?

Emerging PARPi-based neoadjuvant and combination regimens in ovarian cancer: Where are we heading?

PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor.

Update on first-line PARPi maintenance in ovarian cancer: Where are we now?

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Ovarian cancer is a clinically aggressive disease

- Ovarian cancer has the **highest mortality rate** of all gynaecological cancers[1]
- More than 50% of patients have distant metastases at diagnosis, and roughly 70% will die within 5 years[2]

- **Over 300,000** patients are estimated to be diagnosed with ovarian cancer each year[1]
- Globally, ovarian cancer results in **over 200,000 deaths** each year[1]
- Ovarian cancer is the **8th** most common cause of cancer related deaths in women globally[1]
- In Europe, an estimated **66,693** people were diagnosed with ovarian cancer in 2020[1]

1. Global Cancer Observatory: Cancer Today. 2020. Available at: https://gco.iarc.fr/today (accessed 11 April 2023); 2. Gardner AB, et al. *Clin Exp Metastasis*. 2020;37:107–13.

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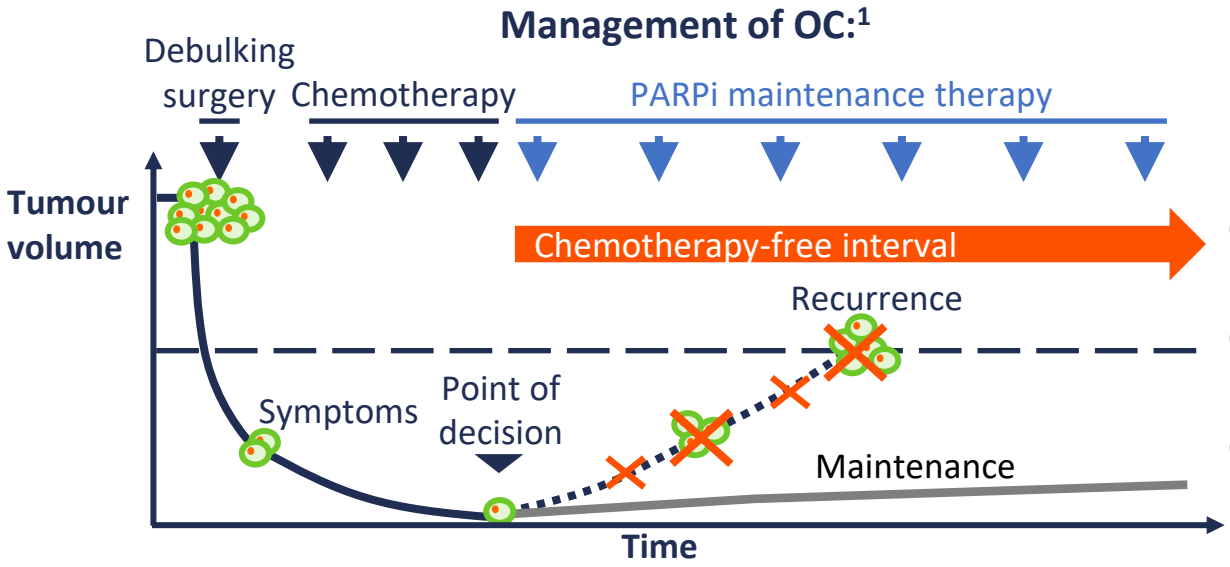
The ovarian cancer challenge: Excellent response to chemotherapy, frequent recurrences



Goals of maintenance therapy:

1. Prolong benefit following surgery and chemotherapy
2. Improve survival (PFS and OS)
3. Manage toxicity and have no negative effects on QoL

>70% of patients with advanced OC will recur within 3–5 years in the absence of 1L maintenance therapy[2,3]

1L, first-line; OC, ovarian cancer; OS, overall survival; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PFS, progression-free survival; QoL, quality of life.

1. DiSilvestro P, Alvarez Secord A. *Cancer Treat Rev.* 2018;69:53–65; 2. Ledermann JA, et al. *Ann Oncol.* 2013;24:vi24–32; 3. du Bois A, et al. *Cancer.* 2009;115:1234–44.

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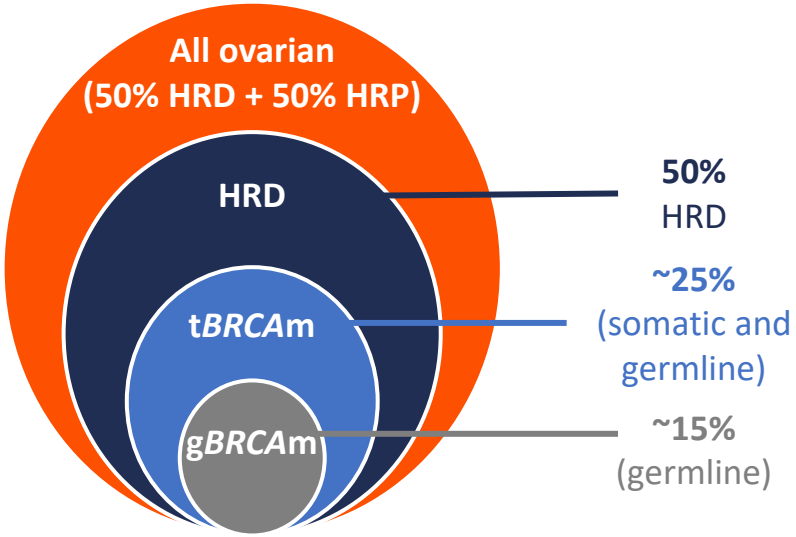
Exploiting biomarker subgroups in high-grade serous ovarian cancer to optimize treatment

Half of high-grade serous ovarian cancers exhibit a high degree of genomic instability due to deficiencies in homologous recombination repair pathway genes[1]



50% are HRD including *BRCA*m, *BRCA*1/2 and *RAD51* promoter methylation, *BRIP1*, and other genes involved in homologous recombination[1,2]

~25% are t*BRCA*m (somatic or germline)[1]

~15% are g*BRCA*m[1]

BRCA, breast cancer gene; BRIP1, BRCA1-interacting protein; g, germline;
HRD, homologous recombination repair deficient; HRP, homologous recombination repair proficient; mutation; t, tumour.

1. Konstantinopoulos PA, et al. *J Clin Oncol.* 2020;38:1222–45; 2. Cancer Genome Atlas Research Network. *Nature.* 2011;474:609–15.

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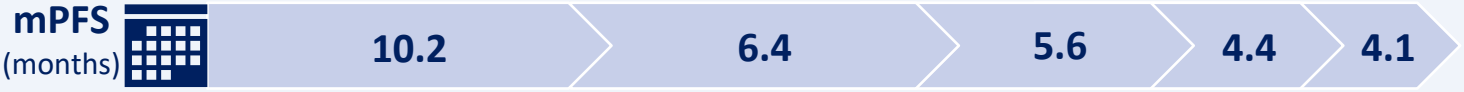
Relapse and survival rates remain clinically challenging in AOC

Without maintenance therapy, PFS shortens with each recurrence[1]



1L PARPi maintenance confers survival benefit,[2–4] but options following relapse are still needed

mPFS

SOLO1 (at 5 years)[2]
- Olaparib: **56.0** months
- Placebo: **13.8** months
- **HR 0.33** (95% CI 0.25–0.43)

PRIMA (at 3.5 years)[3]
- Niraparib: **13.8** months
- Placebo: **8.2** months
- **HR 0.66** (95% CI 0.56–0.79)

ATHENA-MONO (ITT at 26 months)[4]
- Rucaparib: **20.2** months
- Placebo: **9.2** months
- **HR 0.52** (95% CI 0.40–0.68)

1L, first-line; AOC, advanced ovarian cancer; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; m, median; PARPi, poly(adenosine phosphate-ribose) polymerase inhibitor; PFS, progression-free survival.

1. Hanker LC, et al. *Ann Oncol.* 2012;23:2605–12; 2. Banerjee S, et al. *Lancet Oncol.* 2021;22:1721–31; 3. Gonzalez-Martin AJ, et al. *Ann Oncol.* 2022;33(Suppl. 7):S235–82; 4. Monk BJ, et al. *J Clin Oncol.* 2022;40:3952–64.

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Seminal OS in patients who received olaparib: SOLO1/GOG 3004

Mathews C, et al.

Analysis of 7-year OS from the SOLO1 trial, investigating maintenance olaparib in patients with newly diagnosed AOC and a *BRCA*m

N=391

- FIGO stage III–IV, serious or endometrioid ovarian, peritoneal or fallopian tube cancer
- With *BRCA*m
- Cytoreductive surgery
- CR or PR after Pt-ChT

2:1 randomization
N=391

Stratified by Pt-ChT response

For ≤2 years or until disease progression

- **Olaparib** n=260
- **Placebo** n=131

Outcome measures

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, TFST, TSST, safety

	Olaparib (n=260)	Placebo (n=131)
*BRCA1*m	73.5%	69.5%
*BRCA2*m	25.4%	30.5%
*BRCA1*m + *BRCA2*m	1.2%	0%

AOC, advanced ovarian cancer; BRCAm, breast cancer gene mutation; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; PFS, progression-free survival; PR, partial response; Pt-ChT, platinum-based chemotherapy; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

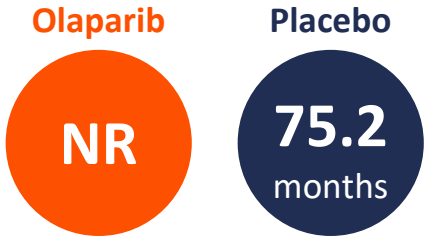
Mathews C, et al. Presented by DiSilvestro P at: SGO 2023 Annual Meeting, Tampa, FL, USA. 25–28 March 2023. Presentation 215.

Seminal OS in patients who received olaparib: SOLO1/GOG 3004

Mathews C, et al.

SOLO1 primary analysis: olaparib prolonged median PFS compared with placebo (NR vs 13.8 months; p<0.001)

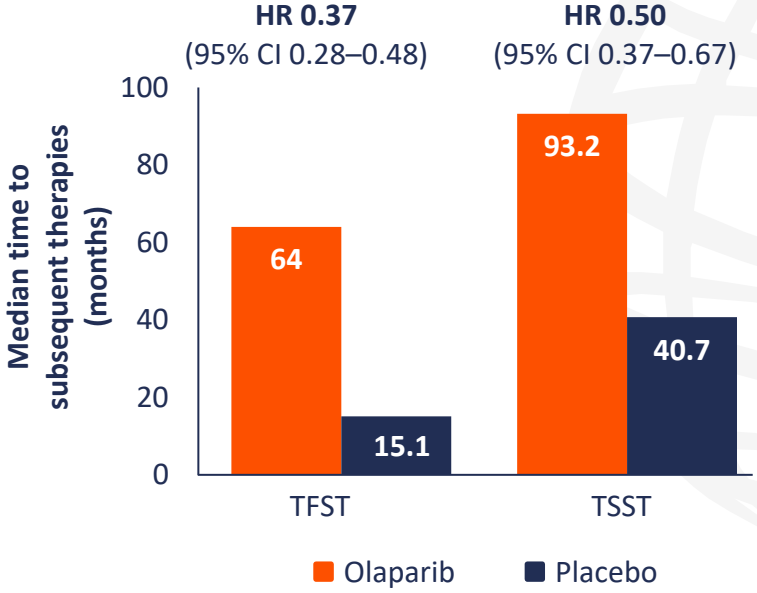
OS after 7-year follow-up



HR 0.55
(95% CI 0.40–0.76; p=0.0004)*

44.3% of patients in the placebo group received a subsequent PARPi, compared with 14.6% in the olaparib group

Effect of olaparib therapy on time to subsequent therapies



*p<0.0001 required to declare statistical significance.
CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PFS, progression-free survival; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.
Mathews C, et al. Presented by DiSilvestro P at: SGO 2023 Annual Meeting, Tampa, FL, USA. 25–28 March 2023. Presentation 215.

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CYP modulating medications in 1LM PARPi-eligible patients

Chase D, et al.

Retrospective cohort study to quantify proportion of patients with AOC receiving cytochrome P450 modulating medications who are eligible for PARPi therapy in the 1LM setting

N=1,459 initiated or eligible

- Ovarian, fallopian tube, peritoneal or other
- female genital cancer
- Advanced disease or epithelial histology
- Adult patients completing 1L Pt-based regimen
- Initiated or eligible to initiate 1LM PARPi monotherapy

Eligible patients split into two cohorts (N=1,411)

PARPi (n=158)
Initiated 1L PARPi monotherapy

PARPi-eligible (n=1,253)
Did not initiate PARPi therapy (but eligible)

Outcome measures

Proportion of patients with AOC receiving CYP-modulating (inhibiting/inducing) medications who were eligible for PARPi therapy, and their demographic and clinical characteristics

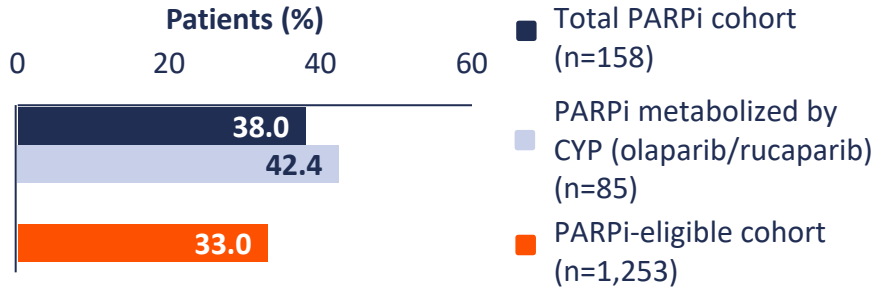
1L, first-line; AOC, advanced ovarian cancer; CYP, cytochrome P450; M, maintenance; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; Pt, platinum.

Chase D, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 2200.

CYP modulating medications in 1LM PARPi-eligible patients

Chase D, et al.

Patients who received strong/moderate CYP i/i mediations



Antiemetics, followed by antibiotics were the most commonly used strong CYP i/i medications across both cohorts

Many patients with AOC received strong/moderate CYP i/i medications, which could increase the risk of DDIs that may impact PARPi efficacy

Baseline demographic and clinical characteristics

	PARPi cohort (n=158)	PARPi-eligible cohort (n=1,253)
Median age	63.0	64.0
Ethnicity, %		
Hispanic/Latino	3.8	4.1
African American	NR*	6.1
Asian	NR*	2.0
White	68.4	59.1
Other/Unknown	24.1	28.7
PARPi maintenance therapy, %		
Olaparib	48.7	-
Niraparib	46.2	-
Rucaparib	5.1	-
Stage at diagnosis, %		
Stage I	0	1.1
Stage II	0	1.8
Stage III	9.5	8.6
Stage IV	90.5	88.1
Unknown	0	0.4

*n <5, thus not reported to maintain patient confidentiality.

AOC, advanced ovarian cancer; CYP, cytochrome; DDI, drug–drug interactions; i/i, inhibiting/inducing; NR, not reported; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor.

Chase D, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 2200.

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Impact of dose modifications on the efficacy of niraparib

Zhu J, et al.

Post hoc analysis of the phase III RCT PRIME to understand the impact of dose modification due to TEAEs on the efficacy of niraparib in patients with newly diagnosed AOC

N=384 randomized

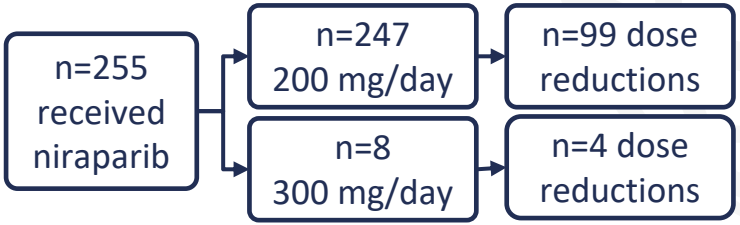
FIGO stage III–IV ovarian cancer

- Primary or interval cytoreductive surgery
- CR or PR to 1L ChT

Outcome measures

- **PRIME primary endpoint:** PFS
- **Post hoc analysis:** PFS and HRs of **TEAE-caused** vs **no TEAE-caused** dose reductions in niraparib-treated patients

Treatment arms and dose reductions

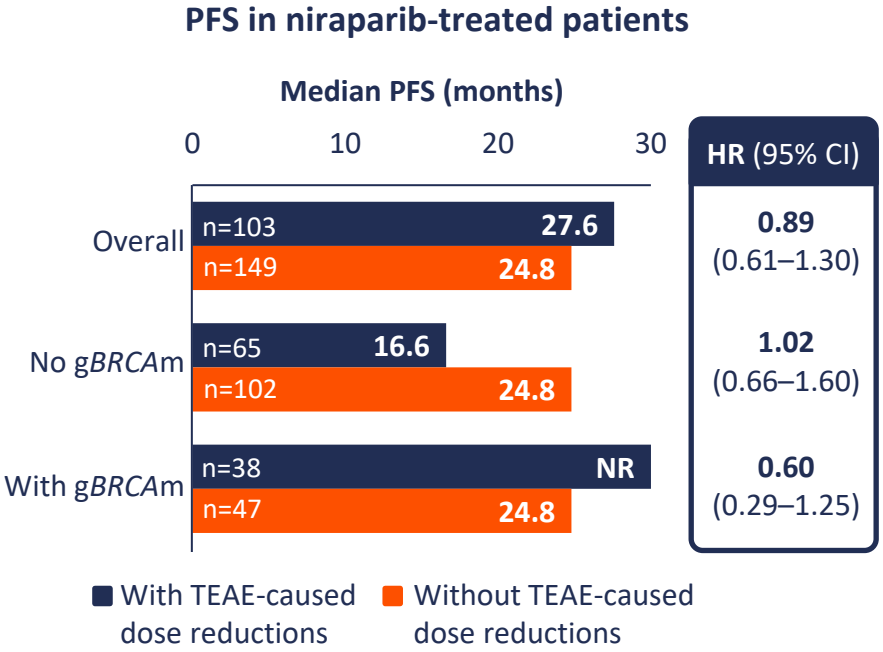


1L, first-line; AOC, advanced ovarian cancer; CR, complete response; ChT, chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; PFS, progression-free survival; PR; partial response; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event.

Zhu J, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 1266.

Impact of dose modifications on the efficacy of niraparib

Zhu J, et al.



	With TEAE-caused dose reductions	Without TEAE-caused dose reductions
Median total exposure, months (range)	**21.9** (1.1–37.8)	**17.3** (0.1–38.5)
Median relative dose intensity, % (range)	**58** (26–106)	**100** (98–147)

- Dose modifications due to TEAEs did not impact efficacy of niraparib in patients with newly diagnosed AOC
- Median PFS was comparable between groups regardless of g*BRCA*m status

AOC, advanced ovarian cancer; gBRCAm, germline breast cancer gene mutation; CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Zhu J, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 1266.

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Risk factors for 1L PARPi maintenance failure: GORILLA-3004

Kim NK, et al.

Multicentre, retrospective study to identify risk factors for 1L PARPi failure in patients with AOC

Jan 2018 – June 2022 → FIGO stage III–IV, epithelial OC → 1L PARPi maintenance therapy

Outcome measure

Risk factors for short PFS of 1L PARPi maintenance

Baseline characteristics (N=191)

- **Median follow-up*:** 9.9 months
- **Histology:** HGSC (92.1%); clear cell (3.7%); endometrioid (1.6%); other (2.6%)
- ***BRCA* mutation:** 63.4%
- **Primary treatment:** PDS: 60.2%; NAC: 37.2%; palliative ChT 5: 2.6%

*Follow-up from the PARPi initiation. 1L, first-line; AOC, advanced ovarian cancer;
BRCA, breast cancer gene; FIGO, International Federation of Gynecology and Obstetrics; ChT, chemotherapy; HGSC, high-grade serious carcinoma; NAC, neoadjuvant chemotherapy; OC, ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PDS, primary debulking surgery; PFS, progression-free survival.
Kim NK, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 1152.

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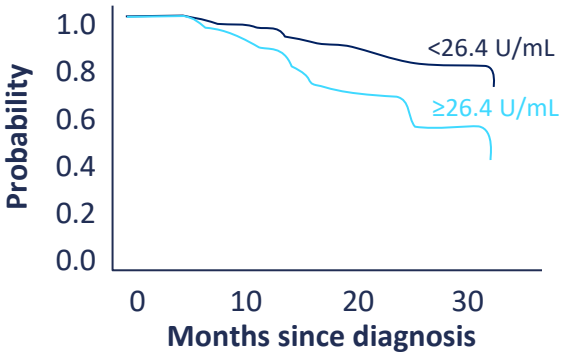
Risk factors for 1L PARPi maintenance failure: GORILLA-3004

Kim NK, et al.

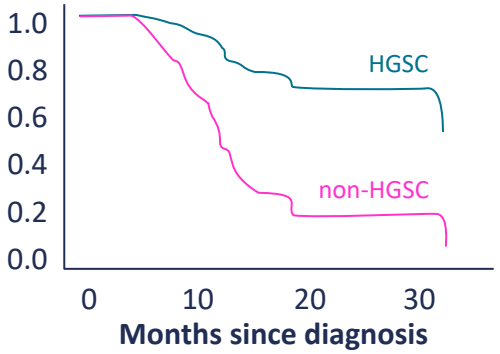
PFS in patients:

With *BRCA*m according to pre-PARPi serum CA-125 levels



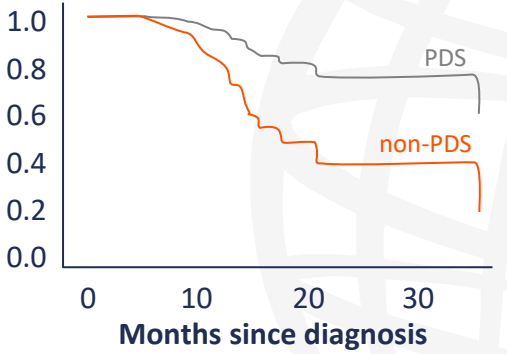
HR: 2.75 (95% CI 1.03–7.39)
p=0.044

Without *BRCA*m according to histologic type



HR: 5.05 (95% CI 1.80–14.18)
p=0.002

By primary treatment



HR: 3.36 (95% CI 1.25–9.04)
p=0.016

High pre-PARPi serum CA-125, non-HGSC histology and no *BRCA* mutation may increase the risk of early failure of 1L PARPi

1L, first-line; BRCAm, breast cancer gene mutation; CA-125, cancer antigen 125; CI, confidence interval; HR, hazard ratio; HGSC, high-grade serious carcinoma; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PDS, primary debulking surgery; PFS, progression-free survival.

Kim NK, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 1152.

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Selection and sequencing implications for PARPis in ovarian cancer emerging from the latest data: What should we consider, and when?

Dr Susana Banerjee
The Royal Marsden NHS Foundation Trust
London, UK

Recorded following the SGO Annual Meeting on Women's Cancer 2023, 25–28 March

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Genomic status remains key in frontline clinical decision making

	*BRCA*m	HRD	HRD with *BRCA*wt	HRP
SOLO1 (olaparib)[1] **5-year follow-up** HR for PFS (95% CI)	**0.33** (0.25–0.43)	-	-	-
PRIMA (niraparib)[2] **3.5-year follow-up** HR for PFS (95% CI)	**0.45** (0.32–0.64)	-	**0.66** (0.44–1.00)	**0.65** (0.49–0.87)
PAOLA-1 (olaparib + bevacizumab)[3] HR for disease progression or death (95% CI)	**0.31** (0.20–0.47)	**0.33** (0.25–0.45)	**0.43** (0.28–0.66)	**1.00** (0.75–1.35)
ATHENA-MONO (rucaparib)[4] HR for PFS (95% CI)	**0.40** (0.21–0.75)	**0.47** (0.31–0.72)	**0.58** (0.33–1.01)	**0.65** (0.45–0.95)
	Standard of care for all *BRCA*m patients?	**Significant benefit in HRD disease?**		**Niraparib and rucaparib can be considered in HRP disease?**

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination repair deficient; HRP, homologous recombination repair proficient; m, mutation; PFS, progression-free survival; wt, wild type.

1. Banerjee S, et al. *Ann Oncol.* 2020;31(Suppl. 4):S551–89; 2. Gonzalez-Martin AJ, et al. *Ann Oncol.* 2022;33(Suppl. 7):S235–82; 3. Ray-Coquard I, et al. *N Engl J Med.* 2019;381:2416–28; 4. Monk BJ, et al. *J Clin Oncol.* 2022;40:3952–64.

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PARPi selection and sequencing decisions can be complex

Patient status and clinical characteristics[1–3]

- Comorbidities (hypertension; thromboembolism)
- FIGO staging
- Prior therapies and surgical outcome(s)
- Timing and site of recurrence
- Other treatment options (surgery; NACT)

Molecular pathology and genomics[1–4]

- *BRCA1/2* mutation status
- HRR pathway status (HRD vs HRP)
- Genomic reversions

Treatment considerations[1–3]

- AE risk(s) and safety profile
- Convenience (dosing; route of administration)
- Patient preference(s) and clinician experience
- Other treatment options (surgery; NACT)
- Clinical trial eligibility for investigational agent(s)

AE, adverse event; BRCA, breast cancer gene; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination repair deficient; HRP, homologous recombination repair proficient; HRR, homologous recombination repair; NACT, neoadjuvant chemotherapy; PARP, poly (adenosine diphosphate-ribose) polymerase. 1. Nero C, et al. *Cancers (Basel).* 2021;13:1298; 2. Mirza MR, et al. *Ann Oncol.* 2020;31:1148–59; 3. Madariaga A, et al. *Int J Gynecol Cancer.* 2020;30:903–15; 4. Cook SA, Tinker AV. *BioDrugs.* 2019;33:255–73.

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Niraparib final OS and long-term safety: ENGOT-OV16/NOVA

Matulonis UA, et al.

Final updated OS and long-term safety results from phase III trial investigating niraparib maintenance therapy in patients with Pt-sensitive recurrent OC

N=553

- Recurrent ovarian, fallopian tube or primary peritoneal cancer
- CR or PR (≥6 months) to ≥2L Pt-ChT

- g*BRCA*m
- Non-g*BRCA*m
  - HRD
  - HRP

Outcome measures

- **Primary endpoint:** PFS
- **Secondary endpoints:** Final OS in both cohorts and in the non-g*BRCA*m cohort by HRD status, CFI, TFST, PFS2, TSST

Additional trial information

- OS data matured (>60%) 1 October 2020
- FDA recommended further data retrieval
- Data cut-off extended by 6 months, up to the date of study unblinding

2L, second-line; CFI, chemotherapy-free interval; ChT, chemotherapy; CR, complete response; FDA, US Food and Drug Administration; gBRCAm, germline breast cancer gene mutation; HRD, homologous recombination deficient; HRP, homologous recombination proficient; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression or death; PR, partial response; Pt, platinum; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

Matulonis UA, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 6.

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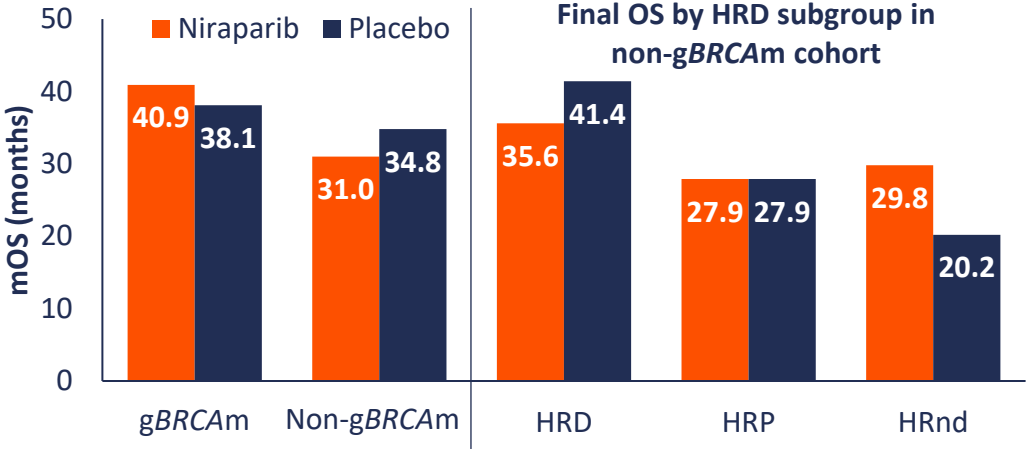
Niraparib final OS and long-term safety: ENGOT-OV16/NOVA

Matulonis UA, et al.

HR (95% CI)	0.85 (0.61–1.20)	1.06 (0.81–1.37)	1.29 (0.85–1.95)	0.93 (0.61–1.41)	0.62 (0.29–1.35)



Other secondary efficacy endpoints

CFI, TFST, PFS2, and TSST, demonstrated a **persistent treatment effect in favour of niraparib** in both the g*BRCA*m and non-g*BRCA*m cohorts

Safety profile

- No new safety signals detected
- Overall incidence of MDS/AML niraparib: 3.8% vs placebo: 1.7%
- One additional case of MDS/AML was reported in the g*BRCA*m cohort

Analyses were confounded by imbalances in post-progression therapy (including subsequent PARPi) by treatment arm in both g*BRCA*m and non-g*BRCA*m cohorts, including HRD subgroup

Data cut-off: 31 March 2021. AML, acute myeloid leukaemia; CFI, chemotherapy-free interval; CI, confidence interval; gBRCAm, germline breast cancer gene mutation; HR, hazard ratio; HRD, homologous recombination deficient; HRnd, homologous recombination not determined; HRP, homologous recombination proficient; MDS, myelodysplastic syndrome; mOS, median OS; OS, overall survival; PFS2, time to second progression or death; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

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PARPis after PARPis in patients with recurrent EOC

Yuan H, et al.

Real-world study investigating the treatment patterns and outcomes in patients with recurrent EOC treated with PARPis after previous PARPi therapy in China

N=49

- Recurrent primary EOC
- Received PARPis in ≥2 lines of therapy

Outcome measures

- Treatment patterns
- TTNT

Patient characteristics

- 49.0% (n=24) *BRCA1/2* mutation
- 63.3% (n=31) two lines of PARPi maintenance treatment
- 28.5% (n=14) one line of PARPi maintenance and one line as upfront treatment
- 8.2% (n=4) two lines of PARPi as upfront treatment

BRCA, breast cancer gene; EOC, epithelial ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; TTNT, time to next treatment.

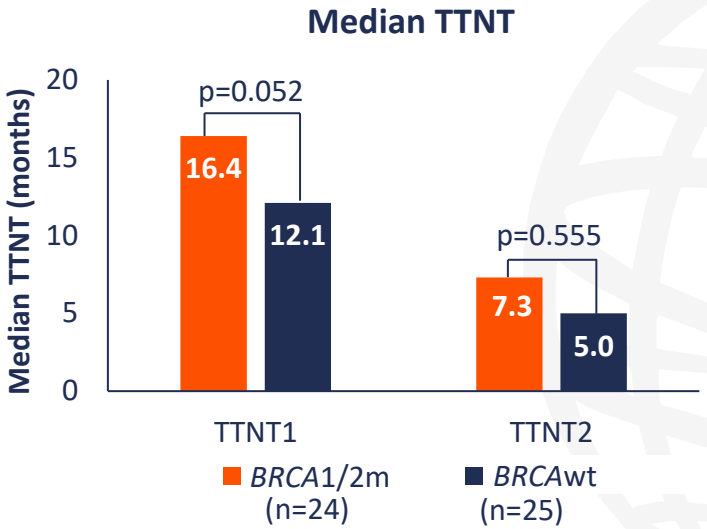
Yuan H, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 1270.

PARPis after PARPis in patients with recurrent EOC

Yuan H, et al.

Median duration of treatment in entire cohort

- PARPi1: 11.2 months (range 2.0–33.5 months)
- PARPi2: 4.6 months (range 1.0–16.7 months)
- 88.9% of patients (32/36) who discontinued PARPi2 (n=36) had a longer duration of PARPi1 than PARPi2



BRCA1/2m, breast cancer gene 1/2 mutation; BRCAwt, BRCA wild-type; EOC, epithelial ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; TTNT, time to next treatment.

Yuan H, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 1270.

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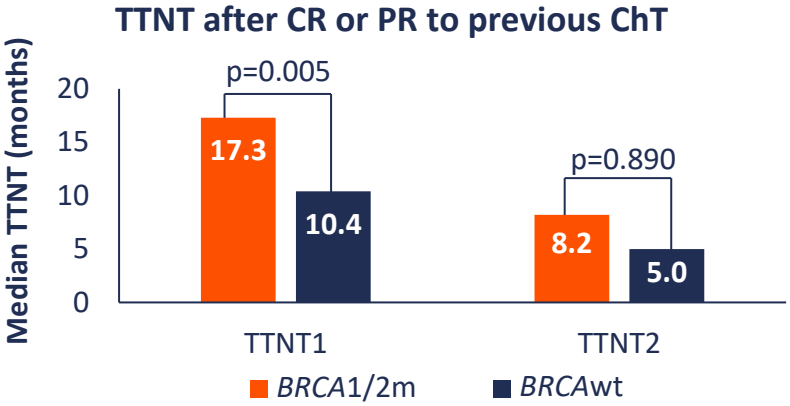
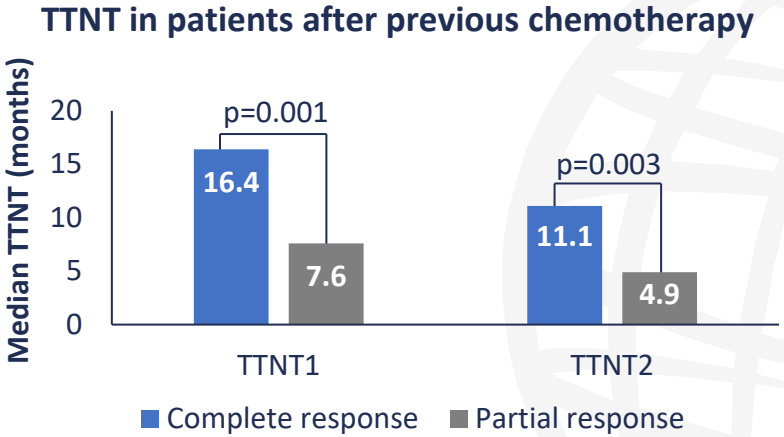
PARPis after PARPis in patients with recurrent EOC

Yuan H, et al.

Response after two lines of maintenance treatment following CR or PR to previous ChT (n=31)

- **TTNT1**: 12.4 months
- **TTNT2**: 7.7 months





Patients with PARPi-resistant, recurrent EOC may derive benefit from PARPi re-treatment, especially for those with a CR to last ChT

BRCA1/2m, breast cancer gene 1/2 mutation; BRCAwt, BRCA wild-type; ChT, chemotherapy; CR, complete response; EOC, epithelial ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PR, partial response; TTNT, time to next treatment.

Yuan H, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 1270.

US real-world data insights: Lessons for genetic testing

Folsom SM, et al.

Retrospective cohort study evaluating impact of FDA-approved 1LM PARPi on genetic testing trends in OC

N=478

Patients diagnosed with OC 2018–2021 (Pittsburgh Medical Center, USA)

2018 cohort: Pre-approval
2019–2021 cohort: Post-approval

Patient age

61.8 years
(range: 16–95)

Stage at diagnosis

Stage I	25.6%
Stage II	10.2%
Stage III	44.6%
Stage IV	19.6%

Histology

Serous	61.1%
Mucinous	8.8%
Endometrioid	11.7%
Clear cell	10.0%
Carcinosarcoma	5.6%
Other	2.7%

1LM, first-line maintenance; FDA, US Food and Drug Administration; OC, ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor.
Folsom SM, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 2158.

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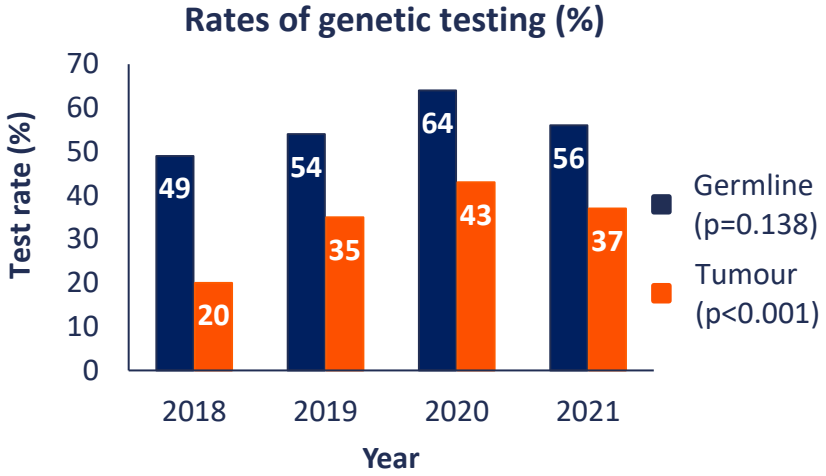
US real-world data insights: Lessons for genetic testing

Folsom SM, et al.

Tumour testing increased significantly



Shorter time to testing in the 2019–2021 cohort

	2018 cohort		2019–2021 cohort	
Germline:	20.02 months	vs	7.79 months	HR 0.66 (95% CI 0.50–0.87)
Tumour:	9.83 months	vs	5.98 months	HR 0.44 (95% CI 0.28–0.63)

Despite improvements in the timeliness and rates of genetic testing following FDA approval of 1LM PARPi, many patients diagnosed with OC still do not receive germline or tumour testing

1LM, first-line maintenance; CI, confidence interval; FDA, US Food and Drug Administration; HR, hazard ratio; OC, ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor.

Folsom SM, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 2158.

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US real-world data insights: Lessons for equitable access

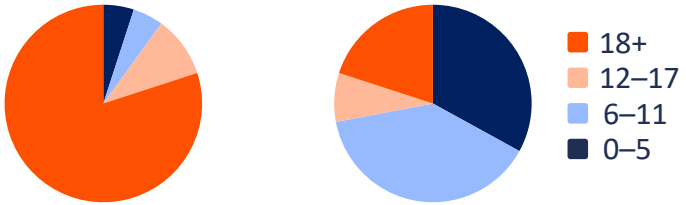
Dottino JA, et al.

Describe the socioeconomic, demographic and clinical characteristics of patients with OC who received PARPi

N=12,801 | Commercial insurance and Medicare Advantage claims database | Diagnosed with OC (Jan 2015 – Sept 2021) | 2015–16: **Initial approval period** 2017–21: **Expanded indications**

Time to PARPi initiation decreased

Proportion of women starting PARPi (%)
by month post-diagnosis



Initial approval period cohort | **Expanded indications cohort**

Trends in PARPi use over time

	Initial approval era cohort	vs	Expanded indications cohort
Received PARPi	**7.3%**		**10.6%**
Less likely to receive PARPi	**Older women** OR 0.74; 95% CI 0.68–0.82		**Less education** OR 0.87; 95% CI 0.78–0.97

- PARPi use increased over time, with patients receiving PARPi sooner post-diagnosis as indications expanded
- Older age and lower education were associated with lower likelihood for receiving PARPi

CI, confidence interval; OC, ovarian cancer; OR, overall response; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor.
Dottino JA, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 2139.

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Emerging PARPi-based neoadjuvant and combination regimens in ovarian cancer: Where are we heading?

Prof. Frederik Marmé
University of Heidelberg,
Heidelberg, Germany

Recorded following the SGO Annual Meeting on Women's Cancer 2023, 25–28 March

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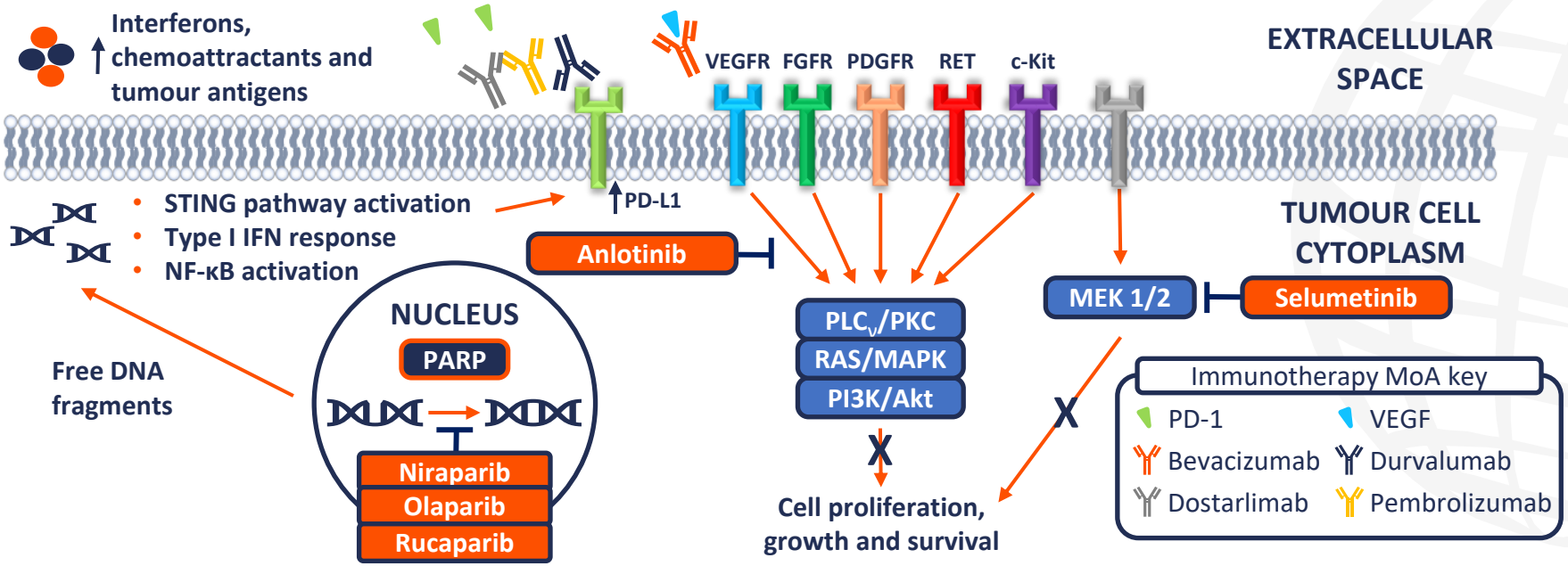
Combination therapies may help to improve outcomes in OC

Improved understanding of the genomic landscape and role of the immune microenvironment opens up potential new combination approaches for PARP inhibitors plus ICIs



Akt, protein kinase B; FGFR, fibroblast growth factor receptor; ICI, immune checkpoint inhibitor; IFN, interferon; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MoA, mechanism of action; NF-κB, nuclear factor kappa B; OC, ovarian cancer; PARP, poly(adenosine diphosphate-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; PD-(L)1, programmed death-(ligand) 1; PI3K, phosphoinositide 3-kinase; PLC_{γ}, phospholipase γ 1; PKC, protein kinase C; RAS, rat sarcoma protein; VEGF(R), vascular endothelial growth factor (receptor).

1. Franzese O, Graziani G. *Cancer (Basel).* 2022;14:5633; 2. Vikas P, et al. *Front Oncol.* 2020;10:570; 3. Gao Y, et al. *Oncol Lett.* 2020;20:1001–14; 4. Miller CR, et al. *Gynecol Oncol.* 2014;133:128–37; 5. Wang Q, et al. *Signal Transduct Target Ther.* 2020;5:137.

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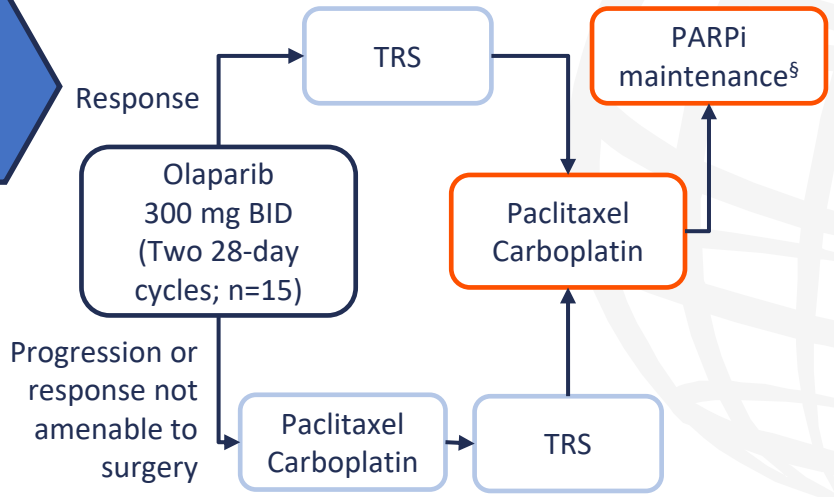
Olaparib in newly diagnosed *BRCA*-mutant OC: NOW

Westin SN, et al.

Single-arm, open-label, pilot study to determine the feasibility of olaparib in the neoadjuvant setting for *BRCA*-mutant ovarian cancer

N=64

- Germline *BRCA1/2, RAD51C/D, PALB2* mutation
- No prior treatment
- Disposition to NACT with planned interval TRS



Outcome measures

Primary:

- Feasibility of olaparib in neoadjuvant setting for *BRCA*-mutant OC
  - Unacceptable toxicity*
  - Disease progression†

Secondary:

- Efficacy‡
- PFS
- Complete pathologic response rate
- Olaparib toxicity in neoadjuvant setting

*Dose interruption >2 weeks, two dose reductions; †RECIST v1.1, new disease, increase CA125 >50%; ‡RECIST v1.1, % of pts able to proceed to interval TRS; §Physician/patient choice.
BRCA, breast cancer gene; BID, twice a day; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PALB2, partner and localizer of BRCA2;
PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PFS, progression-free survival; pts, patients; RECIST, response evaluation criteria in solid tumours;
TRS, tumour reductive surgery.

Westin SN, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 138.

Olaparib in newly diagnosed *BRCA*-mutant OC: NOW

Westin SN, et al.

Safety

- Dose interruption: n=1
- Dose reduction: n=1
- Most common AEs: abdominal pain (33.3%), constipation (26.7%) and anaemia (20.0%)
- Only grade 3/4 AEs reported were 3 patients (20%) with grade 3 anaemia

Efficacy

- Fourteen (93.3%) patients underwent surgery
  - Twelve (85.7%) had no gross residual disease following surgery
  - One patient (8%) had a pathologic complete response
  - All patients had an optimal TRS (<1 cm residual)
- Three patients went directly back to PARPi maintenance after TRS with no intervening ChT

Median turnaround for genetic testing results performed on suspicion of OC was 10 days (range: 5–15)

Neoadjuvant olaparib had an expected safety profile during olaparib window treatment

AE, adverse event; BRCA, breast cancer gene; ChT, chemotherapy; CR, complete response; OC, ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; TRS, tumour reductive surgery.

Westin SN, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 138.

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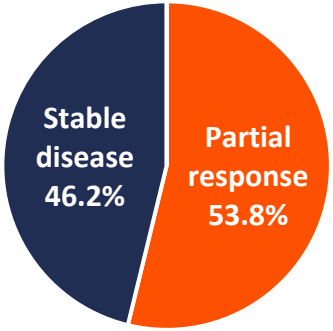
Olaparib in newly diagnosed *BRCA*-mutant OC: NOW

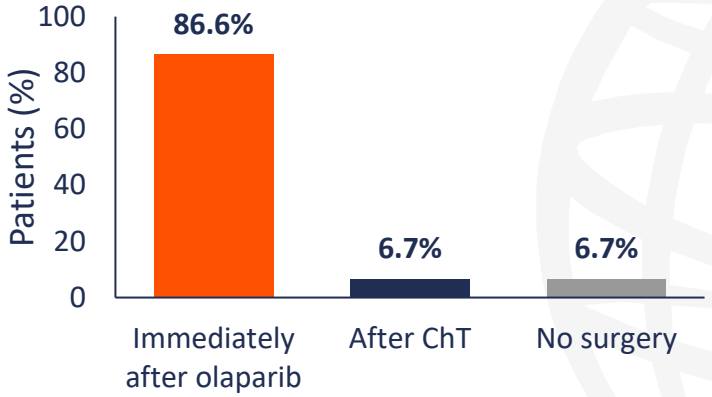
Westin SN, et al.

Response to therapy (n=13)



- Median follow-up = 11.7 months (range 2.0–32.2)
- 12-month PFS probability = 0.81 (CI 0.42–0.95)

Timing of TRS following olaparib (n=15)



- Neoadjuvant olaparib was feasible, with promising surgical outcomes with only two cycles, even in stage IV disease, and an expected safety profile
- Patients were interested in PARPi therapy alone

BRCA, breast cancer gene; CI, confidence interval; ChT, chemotherapy; OC, ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; TRS, tumour reductive surgery.

Westin SN, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 138.

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Selumetinib + olaparib in RAS-aberrant/PARPi-resistant OC: SOLAR

Westin SN, et al.

Phase Ib dose-expansion study of selumetinib + olaparib combination to observe and record toxicity and anti-tumour activity

N=74

- RAS-aberrant OC, endometrial cancer or solid tumour or OC after progression on PARPi
- Unlimited prior therapy
- No prior MEKi

Olaparib 300 mg + selumetinib 75 mg BID

Outcome measures

- Toxicity
- Anti-tumour activity (ORR [CR or PR] and CBR [ORR or SD for 4 months])

Additional trial information

- Toxicity was assessed by CTCAE v4.03
- Response was assessed with RECIST v1.1

BID, twice daily; CBR, clinical benefit rate; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; MEKi, mitogen-activated protein kinase kinase inhibitor; OC, ovarian cancer; ORR, objective response rate; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PR, partial response; RAS, rat sarcoma protein; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Westin SN, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 218.

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Selumetinib + olaparib in RAS-aberrant/PARPi-resistant OC: SOLAR

Westin SN, et al.

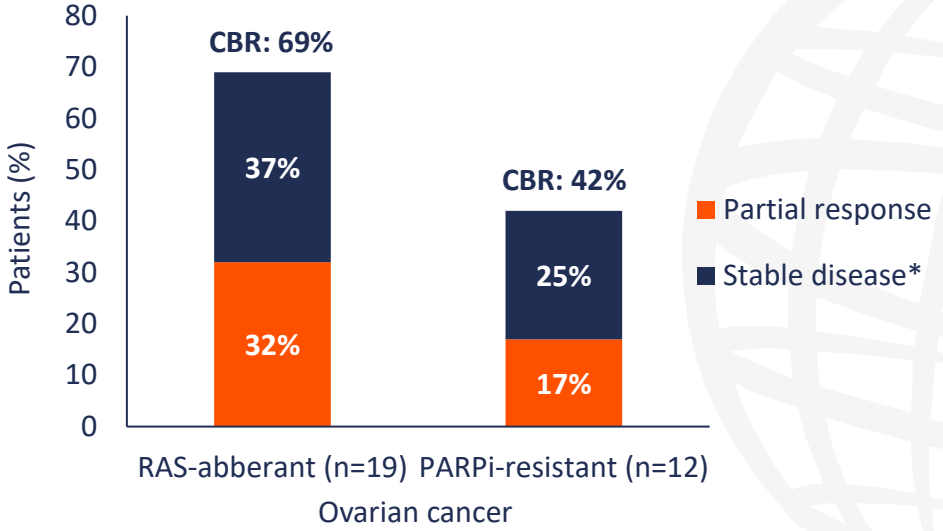
Safety profile (n=81)

- Most common AEs (any grade):
  - Nausea: 75%
  - Fatigue: 62%
  - Anaemia: 59%
- Most common AEs (grade 3/4):
  - Anaemia: 12%
  - Fatigue: 5%
  - Acneiform rash: 5%
  - Neutropenia: 5%

Dose interruptions and reductions (n=88)

- Dose interruptions: 59%
- Dose reductions: 34%
- Discontinuations: 8%

Response to therapy



Of 19 patients with RAS aberrant OC, 9 were LGSOC.
Clinical benefit: 77% (7/9; PR=44%, SD*=33%)

*Stable disease measured after ≥4 cycles.

AE, adverse event; CBR, clinical benefit rate; LGSOC, low-grade serous ovarian cancer; OC, ovarian cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PR, partial response; RAS, rat sarcoma protein; SD, stable disease.

Westin SN, et al. Presented at: SGO Annual Meeting on Women's Cancer, Tampa, FL, USA. 25–28 March 2023. Presentation 218.

PARPi + immunotherapy combination in OC

Phase III trials are underway for PARPi combination therapies with immunotherapy

Trial	KEYLYNK-001 NCT03740165	FIRST NCT03602859	ATHENA-Combo NCT03522246	DUO-O NCT03737643
Combination treatment	Olaparib + pembrolizumab	Niraparib + dostarlimab	Rucaparib + nivolumab	Olaparib + durvalumab + bevacizumab
Patient population	*BRCA* non-mutated advanced EOC	Newly diagnosed advanced non-mucinous EOC	Newly diagnosed OC	Newly diagnosed advanced OC
Primary outcome	PFS	PFS	PFS	PFS
Study completion	May 2025	June 2026	December 2030	May 2028

BRCA, breast cancer gene; EOC, epithelial ovarian cancer; OC, ovarian cancer; PFS, progression-free survival.

1. ClinicalTrials.gov. NCT03740165; 2. ClinicalTrials.gov. NCT03602859; 3. ClinicalTrials.gov. NCT03522246; 4. ClinicalTrials.gov. NCT03737643.
All clinical trials searchable by NCT number. Available at: https://clinicaltrials.gov/ct2/home (accessed 11 April 2023).

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Expanding directions for combination therapy in OC

Trials are underway for combination therapies in the first-line, maintenance and neoadjuvant setting

Combination treatment	**Niraparib + anlotinib maintenance retreatment** (NCT05385068; phase II)[1]	**Niraparib + anlotinib based on CA-125 level in 1L** (NCT05311579; phase II)[2]	**Niraparib vs Pt-taxane doublet ChT as neoadjuvant treatment** (OPAL-C, NCT03574779; phase II)[3]
Patient population	**Pt-sensitive recurrent OC**	**Newly diagnosed OC**	**Newly diagnosed OC**
Outcome measures	• **Primary:** ◦ PFS • **Secondary:** ◦ PFS rate at 6 months ◦ TFST ◦ OS ◦ Safety	• **Primary:** ◦ PFS • **Secondary:** ◦ PFS by *BRCA*m/*BRCA*wt ◦ TFST ◦ OS ◦ Safety	• **Primary:** ◦ Pre-IDS unconfirmed ORR • **Secondary:** ◦ PFS ◦ PFS rate at 12, 18 and 24 months ◦ OS ◦ TFST ◦ Safety
Study completion	**December 2024**	**August 2024**	**May 2026**

1L, first-line; BRCA(m/wt), breast cancer gene (mutation/wild-type); CA-125, cancer antigen 125; ChT, chemotherapy; IDS, interval debulking surgery; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Pt, platinum; TFST, time to first subsequent therapy.

1. Jin Y, et al. Presented at: SGO 2023, Tampa, FL, USA. 25–28 March 2023. Presentation 1265; 2. Li L, et al. Presented by Wu M at: SGO 2023, Tampa, FL, USA. 25–28 March 2023. Presentation 1279; 3. Belotte J, et al. Presented by Zeng X at: SGO 2023, Tampa, FL, USA. 25–28 March 2023. Presentation 1252.