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PARP inhibitor first-line maintenance therapy in AOC

PARP inhibitor maintenance therapy significantly improves PFS in patients with newly diagnosed AOC with a germline and/or somatic *BRCA* mutation and/or HRD-positive tumour (but not HRD-negative tumour)[1]

In patients with complete or partial response to first-line platinum-based chemotherapy

Niraparib

irrespective of
*BRCA*m or HRD status[2,3]

PRIMA[6]

Olaparib

with germline
or somatic *BRCA*m[4,5]

SOLO-1[7]

Olaparib plus bevacizumab

HRD+ status defined as *BRCA*m
and/or genomic instability[4,5]

PAOLA-1[8]

1. Gulia S, et al. *ESMO Open.* 2022;7:100558; 2. EMA. Niraparib SmPC; 3. FDA. Niraparib PI; 4. EMA. Olaparib SmPC; 5. FDA. Olaparib PI;
6. González-Martín A, et al. *N Engl J Med.* 2019;381:2391–402; 7. Moore K, et al. *N Engl J Med.* 2018;379:2495–505; 8. Ray-Coquard I, et al. *N Engl J Med.* 2019;381:2416–28;
EMA SmPC and FDA PI available at: EMA www.ema.europa.eu/ and www.fda.gov/ (accessed 26 October 2022).

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Disease recurrence and poor survival rates remain challenging

AOC has a 5-year survival rate of 17%[1]

Long-term follow-up data on survival benefit with PARPi maintenance are emerging[2,3]

SOLO-1 7-year follow-up[2]

Patients alive at 7 years	Olaparib		Placebo
	67.0%	vs	**46.5%**

ENGOT-OV16/NOVA 6-year follow-up[3]

Mean OS	with g*BRCA*m			without g*BRCA*m		
	Niraparib		**Placebo**	**Niraparib**		**Placebo**
	45.9 months	vs	**43.2** months	**38.5** months	vs	**39.1** months

Increasing awareness of *BRCA* and HRD testing in patients with AOC is essential for optimizing treatment decision-making and improving clinical outcomes[4]

1. Huang J, et al. *Cancers (Basel).* 2022;14:2230; 2. DiSilvestro P, et al. *J Clin Oncol.* 2022:JCO2201549 (Online ahead of print);
3. Matulonis U, et al. *Gynecol Oncol.* 2021;162(Suppl. 1):S24–5; 4. Goh JCH, et al. *Gynecol Oncol Rep.* 2022;42:101028.

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Overview

**PARP inhibitors as first-line maintenance therapy in ovarian cancer:
How can data from the ESGO 23rd European Congress on Gynaecological
Oncology 2022 guide clinical practice?**

- **Part 1:** Latest clinical trial data for PARP inhibitors in the first-line maintenance setting for advanced ovarian cancer

- **Part 2:** Real-world data on the use of PARP inhibitors in the first-line maintenance setting for advanced ovarian cancer

- **Part 3:** Patient-related considerations based on real-world data with PARP inhibitors in the first-line maintenance setting for advanced ovarian cancer

ESGO 23rd European Congress on Gynaecological Oncology 2022

Latest clinical trial data for PARP inhibitors in the first-line maintenance setting for advanced ovarian cancer

ESGO, European Society of Gynaecological Oncology; PARP, poly(adenosine diphosphate-ribose) polymerase.

ATHENA-MONO: Exploratory biomarker analysis

Oaknin A, et al.

Post hoc exploratory genomic analysis to evaluate PFS in certain subgroups of the ATHENA-MONO trial, investigating first-line maintenance therapy with rucaparib

- N=538
- Newly diagnosed, FIGO stage III–IV, high-grade ovarian cancer
- Completed 4–8 cycles of first-line platinum-doublet chemotherapy and surgery (no other prior treatment for ovarian cancer permitted)
- Randomized 4:1 to rucaparib 600 mg or placebo BD
- Treated for 24 months (or until radiographic progression, unacceptable toxicity or other reason for discontinuation)

PRIMARY ENDPOINT: Investigator assessed PFS by RECIST v1.1

Post hoc exploratory genomic analysis endpoints

Evaluation of PFS in subgroups:
- Germline or somatic *BRCA* status
- *BRCA* mutation type, zygosity status and pre-specified non-*BRCA* HRR genes

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ATHENA-MONO: Exploratory biomarker analysis

Oaknin A, et al.

- First-line rucaparib maintenance significantly improved PFS vs placebo, regardless of molecular characteristics
- HR favoured rucaparib in HRD (HR 0.47 [95% CI 0.31–0.72], p=0.0004) and ITT (HR 0.52 [95% CI 0.40–0.68], p<0.0001) groups

Median PFS in patients with deleterious BRCA1/2 mutations (months)

BRCA1	BRCA2
• Rucaparib: NR • Placebo: 13.3 • **HR 0.39** (95% CI 0.14–1.08)	• Rucaparib: NR • Placebo: 18.8 • **HR 0.46** (95% CI 0.13–1.69)

Median PFS in patients with germline or somatic BRCA mutations (months)

Germline	Somatic
• Rucaparib: NR • Placebo: 18.9 • **HR 0.33** (95% CI 0.10–1.12)	• Rucaparib: NR • Placebo: 23.6 • **HR 0.65** (95% CI 0.18–2.39)

Median PFS in patients non-BRCA HRR gene mutations (months)

- Rucaparib: 20.2
- Placebo: 9.2
- **HR 0.59**
  (95% CI 0.24–1.43)

Confirmed benefit of first-line rucaparib as first-line maintenance in AOC harbouring different types of deleterious mutations in BRCA and non-BRCA HRR genes

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Geneva HRD test: Clinical validation from PAOLA-1

Christinat Y, et al.

Clinically validate the Geneva HRD test using samples from the PAOLA-1 phase III trial

- Samples analysed in the Geneva University Hospitals with the OncoScan™ CNV Assay and an in-house algorithm developed using TCGA data
- Results compared to the Myriad myChoice assay with respect to PFS with olaparib + bevacizumab and placebo + bevacizumab
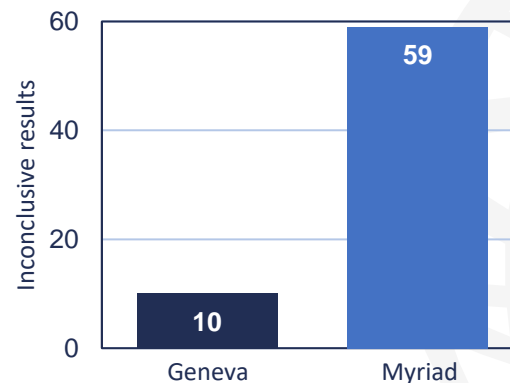
Part of the ENGOT HRD European Initiative

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Geneva HRD test: Clinical validation from PAOLA-1

Christinat Y, et al.

Hazard ratio for PFS by test

	Geneva	Myriad
HRD-positive samples	0.40	0.35
HRD-positive and *BRCA*m samples	0.29	0.31
HRD-positive and *BRCA*wt samples	0.53	0.41
HRD negative samples	1.2	1.1

HRD test failure rate (N=469)

Positive agreement values: 96% (204/213); negative agreement values: 81% (159/197)

The Geneva HRD test is a viable alternative to the Myriad myChoice assay and has demonstrated a lower failure rate. The test can be easily implemented into routine clinical practice

NOGGO-GIS ASSAY: Clinical validation from PAOLA-1

Willing EM, et al.

Part of the ENGOT HRD European Initiative

Evaluate the novel "NOGGO-GIS ASSAY" using samples from the PAOLA-1 trial

- NOGGO-GIS ASSAY is a hybrid capture NGS assay covering 57 genes and approximately 20,000 SNP loci
- Requires 50 ng of genomic DNA extracted from tissue section with at least 30% tumour content
- Low failure rate of ~5%

- Clinically validated using 468 ovarian cancer samples from PAOLA-1 (where Myriad myChoice assay was used)
- Performance characteristics of NOGGO-GIS ASSAY comparable to Myriad assay:
  - Comparable HR for PFS with olaparib + bevacizumab in HRD-positive patients between two assays

Performance characteristics for the NOGGO-GIS ASSAY were comparable to the Myriad myChoice assay; NOGGO-GIS ASSAY is a suitable option for analysis of FFPE samples

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GIScar: A novel academic GIS for ovarian cancers

Leman R, et al.

> Validation of a genomic instability score that could be deployed in academic molecular biology laboratories

- GIScar developed to be used within the constraints of most academic molecular biology laboratories
- Developed using sequencing data from a limited panel of 127 genes
- Technically validated against 146 prospective samples from ovarian tumours with HRD status previously defined by Myriad myChoice assay
- Clinical validation through sequencing 469 DNA tumour samples from PAOLA-1 trial (the tumour classification by GIScar was correlated to olaparib efficacy, as assessed by PFS)

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GIScar: A novel academic GIS for ovarian cancers[1]

Leman R, et al.

PFS in PAOLA-1[2]
(HRD status determined by Myriad myChoice assay)

Clinical validation of GIScar in 469 tumours from PAOLA-1 with PFS data

■ Olaparib + bevacizumab   ■ Placebo + bevacizumab
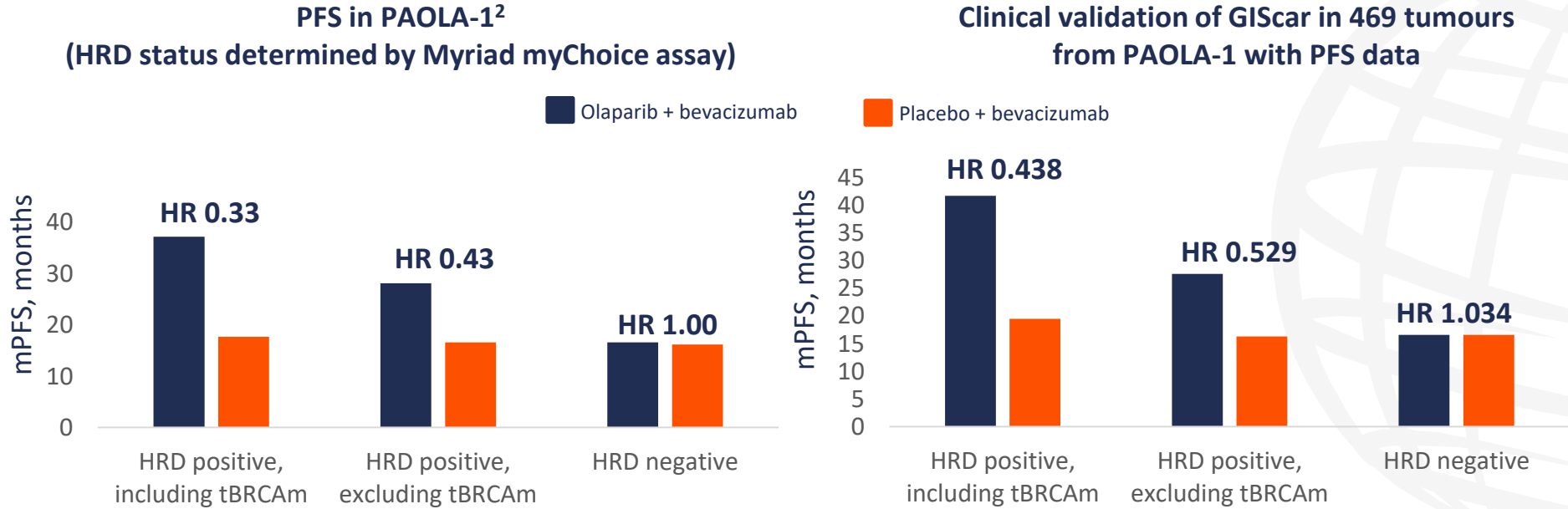
The tumour classification by GIScar is correlated to olaparib efficacy assessed by PFS

GIS, genomic instability score; GIScar, Genomic Instability Scar; HR, hazard ratio; HRD, homologous recombination deficiency; mPFS, median progression-free survival; tBRCAm; tumour BRCA mutation.
1. Leman R, et al. Presented at: ESGO 23rd European Congress on Gynaecological Oncology, Berlin, Germany. 27–30 October 2022. Abstr 935;
2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416–28.

CA125 monitoring and patterns of recurrence

Boccia SM, et al.

Explore the pattern of recurrence in patients with ovarian cancer receiving PARPi maintenance, including concordance between CA125 progression and radiological disease progression

- Retrospective study
- *BRCA* wild-type ovarian cancer
- First recurrence during maintenance with niraparib
- CA125 elevation before starting platinum-based therapy

CT scan every 24 weeks or earlier in case of clinical or CA125 progression ▸ CA125 testing monthly ▸ Pattern of recurrences also collected

CA125 monitoring and patterns of recurrence

Boccia SM, et al.

91 patients progressed after a median recurrence-free interval of 5 months

70% of patients had **concordant** CA125 and clinical RECIST progression

30% of patients had radiological progression without CA125 elevation

7% of patients with peritoneal carcinosis were CA125 negative ($p<0.001$)

69.2% of patients with oligometastases were CA125 negative ($p=0.002$)

Recurrence after niraparib may occur as oligometastatic disease without CA125 rising; CA125 surveillance alone may not be sufficient to detect disease progression in these patients

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Summary

- In ATHENA-MONO, first-line maintenance rucaparib demonstrated PFS benefits compared with placebo in advanced ovarian cancer harbouring *BRCA* and non-*BRCA* HRR gene mutations

- Novel HRD assays have been developed, including the Geneva HRD test, the NOGGO-GIS ASSAY and the GIScar

- All three novel assays have been validated and are viable alternatives to the Myriad myChoice assay (used in PAOLA-1) with comparable sensitivity and accuracy; lower failure rates observed with Geneva HRD test

- Oligometastatic disease recurrence may occur following niraparib therapy without CA125 levels rising. As such, CA125 monitoring alone may be inadequate to detect disease progression

BRCA, breast cancer gene; CA125, cancer antigen 125; GIScar, Genomic Instability Scar; HRD, homologous recombination deficiency; HRR, homologous recombination DNA repair; PFS, progression-free survival.

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ESGO 23rd European Congress on Gynaecological Oncology 2022

Real-world data on the use of PARP inhibitors in the first-line maintenance setting for advanced ovarian cancer

PARP, poly(adenosine diphosphate-ribose) polymerase; ESGO, European Society of Gynaecological Oncology.

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First analysis of the pan-European OVAL-1 RWE study
Lorusso D, et al.

Report real-world clinical outcomes and treatment patterns among patients with t/g*BRCA*-mutated advanced ovarian cancer who received first-line maintenance therapy with olaparib

- N=324 in interim analysis
- Newly diagnosed, FIGO stage III–IV ovarian cancer
- t/g*BRCA*m
- In response after first-line platinum-based chemotherapy
- Received first dose of olaparib in first-line maintenance setting
- Minimum follow-up of 1 year

Endpoint assessment

- **PRIMARY:** PFS, olaparib treatment patterns
- **SECONDARY:** PFS2, response rate, OS, surgical and chemotherapy outcomes, HRU, dose modifications/discontinuations, AEs leading to dose modifications/discontinuations
- **EXPLORATORY:** timing of *BRCA* testing, *BRCA* testing turnaround time
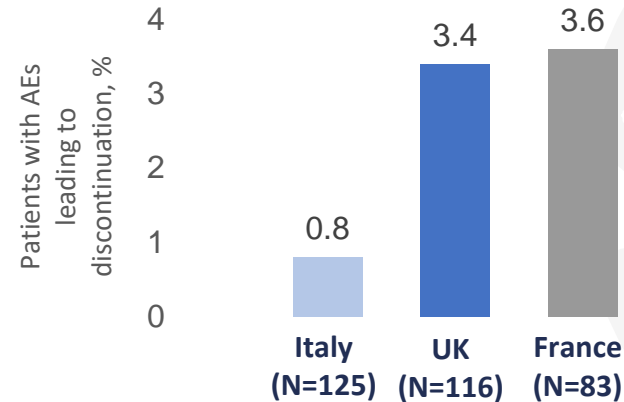
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First analysis of the pan-European OVAL-1 RWE study

Lorusso D, et al.

Results

- Baseline characteristics were similar across patients
- Differences were noted across countries for *BRCA*m testing pathways
- PFS data not mature yet
- Safety profile consistent with data previously reported for maintenance olaparib in this setting

Low discontinuation rates due to AEs for olaparib during first year (%)

Bar chart: Patients with AEs leading to discontinuation, %

- Italy (N=125): 0.8
- UK (N=116): 3.4
- France (N=83): 3.6

Study provides real-world insights into management of advanced ovarian cancer for patients who received olaparib as their first follow-on therapy

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Niraparib maintenance in newly diagnosed AOC
Pautier P, et al.

Report RWD for patients with newly diagnosed advanced ovarian cancer receiving first-line maintenance therapy with niraparib via the French early-access programme

- Patients were ≥18 years with newly diagnosed, high-grade (FIGO stages III and IV) ovarian cancer, including cancer of the fallopian tubes and peritoneum
- Complete or partial response to first-line platinum-based chemotherapy
- Treatment initiated within 8 weeks of finishing chemotherapy
- 67 patients received niraparib

Data collection methods
- Electronic treatment access request forms
- Treatment discontinuation forms
- Follow-up forms
- National pharmacovigilance data

Key patient characteristics
- Median age: 70.7 years
- 72% of patients had undergone prior surgery
- 27% had stage IV disease, of which 36% were inoperable

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Niraparib maintenance in newly diagnosed AOC
Pautier P, et al.

Dosing (data for n=51)
92% initiated niraparib at the 200 mg/day dose
8% initiated niraparib at the 300 mg/day dose

Dose modifications (data for n=34)
56% had ≥1 temporary discontinuation
24% had ≥1 dose reduction

Safety
86 TRAEs occurred in 28/67 patients
Most commonly reported TRAEs

	All grades	Grade 3/4
Thrombocytopenia	25%	7%
Nausea	10%	1%
Abnormal haemaglobin	9%	0%

In a French study, niraparib safety profile using recommended dosing was consistent with clinical trials

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Summary

- The OVAL-1 study provides real-world insights into the use of olaparib in the first-line maintenance setting. Safety data were consistent with the existing profile for olaparib in this setting; discontinuation rates due to AEs were low

- Data from a French early-access programme found that the real-world safety profile of niraparib was consistent with clinical trials

AE, adverse event.

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Patient-related considerations based on real-world data with PARP inhibitors in the first-line maintenance setting for advanced ovarian cancer

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Biomarker testing and first-line maintenance patterns in AOC
Veljovich DS, et al.

Evaluate biomarker testing and treatment patterns in a representative advanced ovarian cancer patient sample managed in routine clinical practice in the USA

- Retrospective, longitudinal cohort study utilizing a nationwide (USA) electronic health record-derived database
- Patients aged ≥18 years diagnosed with advanced ovarian cancer between July 2018 and December 2021
- Biomarker testing defined as evidence of a test for *BRCA*m (germline and/or somatic) or HRD

Testing
- 88% of patients were tested for germline and/or somatic *BRCA*m
- 23% of patients were tested for HRD

Testing rates for *BRCA*m/HRD by year of AOC diagnosis

	*BRCA*m	HRD
2018	81.2%	8.2%
2019	85.2%	16.4%
2020	85.5%	30.0%
2021	87.1%	25.8%

_BRCA_m testing rates were high in patients with AOC, but HRD testing rates were low

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First-line niraparib maintenance: Real-world US study
Salani R, et al.

Characterize real-world patients in the USA with epithelial ovarian cancer prescribed first-line maintenance therapy with niraparib before and after FDA approval

N=374

| Adults diagnosed with EOC between Jan 2011 and Nov 2021 | Prior 1L platinum therapy followed by niraparib 1L maintenance from Jan 2017 | Patients stratified by pre- and post-niraparib approval on 29 Apr 2020 |

Patients grouped according to number of high-risk factors for disease progression or death:
- *BRCA*wt or unknown
- Stage IV disease
- VRD or no surgery
- IDS or no surgery

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First-line niraparib maintenance: Real-world US study
Salani R, et al.

- 90 and 284 patients received first-line niraparib maintenance pre- and post-approval, respectively
- 50.3% of all patients had stage III and 34.8% had stage IV epithelial ovarian cancer at diagnosis, 80.5% had serous histology, 10.2% had *BRCA* mutation

Distribution of patients by total number of high-risk factors among patients with complete data for risk factor classification (n=266)

Total number of high-risk factors	Patients, %
0	NR
1	19.2
2	30.1
3	30.8
4	18.8

Distribution of high-risk factors among patients with complete data for risk factor classification (n=266)

High-risk factors	Patients, %
*BRCA*wt or unknown	89.8
IDS or no surgery	65.8
VRD or no surgery	50.0
Stage IV	41.4

Study is the first to describe characteristics and risk profiles of real-world patients who started niraparib first-line maintenance therapy based on FDA approval status

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VOCAL study: Patient preferences for dosing methods

Chase D, et al.

Describe patient preference in a US study when considering maintenance therapies and active surveillance (no medication) after first-line chemotherapy in advanced ovarian cancer

N=152

Patients completed a two-part TTO exercise assessing:
(1) scenario preference
(2) TTO of preferred scenario vs alternatives

(1) Preferred post-chemotherapy treatment was ranked
- AS only (no medication)
- Pill/tablet/capsule QD
- Pill/tablet/capsule BD
- IV infusion Q3W
- IV infusion Q3W + tablet/capsule BD

Assuming equivalent safety and efficacy for all scenarios

(2) Willingness to stay on preferred scenario with reduced time to progression vs constant (3 years) time prior to disease progression on alternative scenario

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VOCAL study: Patient preferences for dosing methods
Chase D, et al.

(1) Preferred scenario

- AS
- QD
- BD
- IV-Q3W
- IV-Q3W/BD

AS: 44%
QD: 38%
BD: 9%
IV-Q3W: 7%
IV-Q3W/BD: 2%
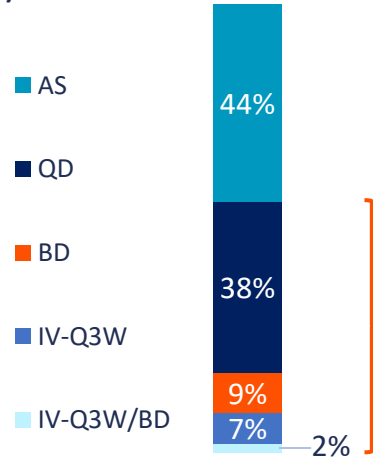
> " *Taking an actual drug/medication makes me feel I am actively doing something to prevent my cancer from coming back* "

66% of respondents who selected active treatment

(2) TTO scores for each scenario (months)

QD	2.3
BD	3.2
IV-Q3W	5.5
AS	6.2
IV-Q3W/BD	7.5

Highest preference

↓

Lowest preference

Most patients preferred active medication (56%) vs AS (44%), mainly because it felt like an active approach against cancer; most patients preferred oral QD therapy as the alternative to their initial choice

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Summary

- HRD testing rates were found to be low in a US real-world study, but have increased with the approval of olaparib + bevacizumab[1]

- VOCAL study showed that most patients with advanced ovarian cancer prefer active medication (usually a pill/tablet/capsule QD) as maintenance therapy vs active surveillance

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Thank you for watching!

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