PARP inhibitors as first-line maintenance therapy in ovarian cancer: How can data from ESGO 2022 guide clinical practice?

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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\(^8\)

AOC, advanced ovarian cancer; BRCA, breast cancer gene; BRCA\(_m\), BRCA mutation; HRD, homologous recombination deficiency; PARP, poly(adenosine diphosphate-ribose) polymerase; PFS, progression-free survival.

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\(^2\)**

<table>
<thead>
<tr>
<th>Patients alive at 7 years</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67.0%</td>
<td>46.5%</td>
</tr>
</tbody>
</table>

**ENGOT-OV16/NOVA 6-year follow-up\(^3\)**

<table>
<thead>
<tr>
<th>with gBRCAm</th>
<th>Niraparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean OS</td>
<td>45.9 months vs 43.2 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>without gBRCAm</th>
<th>Niraparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean OS</td>
<td>38.5 months vs 39.1 months</td>
<td></td>
</tr>
</tbody>
</table>

Increasing awareness of BRCA and HRD testing in patients with AOC is essential for optimizing treatment decision-making and improving clinical outcomes\(^4\)

AOC, advanced ovarian cancer; BRCA, breast cancer gene; gBRCAm, germline BRCA mutation; ENGOT, European Network for Gynaecological Oncological Trial groups; HRD, homologous recombination deficiency; OS, overall survival; PARPi, poly(adenosine phosphate-ribose) polymerase inhibitor.

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

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

<table>
<thead>
<tr>
<th>BRCA1 mutations (months)</th>
<th>BRCA2 mutations (months)</th>
<th>Germline mutations (months)</th>
<th>Somatic mutations (months)</th>
<th>Median PFS in patients non-BRCA HRR gene mutations (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td><strong>BRCA2</strong></td>
<td><strong>Germline</strong></td>
<td><strong>Somatic</strong></td>
<td></td>
</tr>
<tr>
<td>Rucaparib: NR</td>
<td>Rucaparib: NR</td>
<td>Rucaparib: NR</td>
<td>Rucaparib: NR</td>
<td></td>
</tr>
<tr>
<td>Placebo: 13.3</td>
<td>Placebo: 18.8</td>
<td>Placebo: 18.9</td>
<td>Placebo: 23.6</td>
<td>Placebo: 9.2</td>
</tr>
<tr>
<td>HR 0.39</td>
<td>HR 0.46</td>
<td>HR 0.33</td>
<td>HR 0.65</td>
<td>HR 0.59</td>
</tr>
<tr>
<td>(95% CI 0.14–1.08)</td>
<td>(95% CI 0.13–1.69)</td>
<td>(95% CI 0.10–1.12)</td>
<td>(95% CI 0.18–2.39)</td>
<td>(95% CI 0.24–1.43)</td>
</tr>
</tbody>
</table>

**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**

AOC, advanced ovarian cancer; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; HRR, homologous recombination DNA repair; ITT, intention-to-treat; NR, not reached; PFS, progression-free survival.

**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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CNV, copy number variations; ENGOT, European Network for Gynaecological Oncological Trial groups; HRD, homologous recombination deficiency; PFS, progression-free survival; TCGA, The Cancer Genome Atlas.

Geneva HRD test: Clinical validation from PAOLA-1
Christinat Y, et al.

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.

<table>
<thead>
<tr>
<th>HRD status</th>
<th>Geneva</th>
<th>Myriad</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRD-positive samples</td>
<td>0.40</td>
<td>0.35</td>
</tr>
<tr>
<td>HRD-positive and BRCAm samples</td>
<td>0.29</td>
<td>0.31</td>
</tr>
<tr>
<td>HRD-positive and BRCAwt samples</td>
<td>0.53</td>
<td>0.41</td>
</tr>
<tr>
<td>HRD negative samples</td>
<td>1.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

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

HRD test failure rate (N=469)

BRCA, breast cancer gene; BRCAm, BRCA mutated; BRCAwt, BRCA wild-type; HRD, homologous recombination deficiency; PFS, progression-free survival.
NOGGO-GIS ASSAY: Clinical validation from PAOLA-1
Willing EM, et al.

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

FFPE, formalin-fixed paraffin-embedded; HR, hazard ratio; HRD, homologous recombination deficiency; NGS, next-generation sequencing; PFS, progression-free survival; SNP, single nucleotide polymorphisms.
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)
GIScar: A novel academic GIS for ovarian cancers

Leman R, et al.

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

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

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.

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

BRCA, breast cancer gene; CA125, cancer antigen 125; CT, computed tomography; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor.
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.

CA125, cancer antigen 125; RECIST, Response Evaluation Criteria in Solid Tumours.
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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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.
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/gBRCA-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/gBRCAm
- 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

AE, adverse event; BRCA, breast cancer gene; FIGO, The International Federation of Gynecology and Obstetrics; HRU, healthcare resource utilization; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence; t/gBRCAm, tumour or germline BRCA1/2-mutated.

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 BRCAm 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 (%)

- 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

AE, adverse event; BRCAm, breast cancer gene mutation; PFS, progression-free survival; RWE, real-world evidence.

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
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

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>25%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal haemoglobin</td>
<td>9%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

ESGO, European Society of Gynaecological Oncology; PARP, poly(adenosine diphosphate-ribose) polymerase.
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 BRCAm (germline and/or somatic) or HRD

Testing rates for BRCAm/HRD by year of AOC diagnosis

<table>
<thead>
<tr>
<th>Year</th>
<th>BRCAm</th>
<th>HRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>81.2%</td>
<td>8.2%</td>
</tr>
<tr>
<td>2019</td>
<td>85.2%</td>
<td>16.4%</td>
</tr>
<tr>
<td>2020</td>
<td>85.5%</td>
<td>30.0%</td>
</tr>
<tr>
<td>2021</td>
<td>87.1%</td>
<td>25.8%</td>
</tr>
</tbody>
</table>

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

AOC, advanced ovarian cancer; BRCAm, breast cancer gene mutation; HRD, homologous recombination deficiency.

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.

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

1L, first-line; *BRCA*wt, breast cancer gene wild-type; EOC, epithelial ovarian cancer; FDA, US Food & Drug Administration; IDS, interval debulking surgery; VRD, visible residual disease.

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)

<table>
<thead>
<tr>
<th>Total number of high-risk factors</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>1</td>
<td>19.2</td>
</tr>
<tr>
<td>2</td>
<td>30.1</td>
</tr>
<tr>
<td>3</td>
<td>30.8</td>
</tr>
<tr>
<td>4</td>
<td>18.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>High-risk factors</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCAwt or unknown</td>
<td>89.8</td>
</tr>
<tr>
<td>IDS or no surgery</td>
<td>65.8</td>
</tr>
<tr>
<td>VRD or no surgery</td>
<td>50.0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>41.4</td>
</tr>
</tbody>
</table>

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.

BRCA, breast cancer gene; BRCAwt, BRCA wild-type; FDA, US Food & Drug Administration; IDS, interval debulking surgery; NR, not reported; VRD, visible residual disease.
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.

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

N=152

(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.

AS, active surveillance; BD, twice daily; IV, intravenous; Q3W, once every 3 weeks; QD, once daily; TTO, time trade-off.

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

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.

(1) Preferred scenario
- AS: 44%
- QD: 38%
- BD: 9%
- IV-Q3W: 7%
- IV-Q3W/BD: 2%

(2) TTO scores for each scenario (months)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>TTO Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD</td>
<td>2.3</td>
</tr>
<tr>
<td>BD</td>
<td>3.2</td>
</tr>
<tr>
<td>IV-Q3W</td>
<td>5.5</td>
</tr>
<tr>
<td>AS</td>
<td>6.2</td>
</tr>
<tr>
<td>IV-Q3W/BD</td>
<td>7.5</td>
</tr>
</tbody>
</table>

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.
Summary

- HRD testing rates were found to be low in a US real-world study, but have increased with the approval of olaparib + bevacizumab¹

- 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

HRD, homologous recombination deficiency; QD, once daily.

1. FDA. Olaparib PI. Available at: www.fda.gov/ (accessed 26 October 2022).
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Thank you for watching!