Olaparib in ovarian cancer
Content

- Introduction to epithelial ovarian cancer

- PARP inhibitors – therapeutic paradigm in ovarian cancer
  - Biomarkers for PARP sensitivity

- Clinical evidence for Lynparza
Introduction to epithelial ovarian cancer
Ovarian cancer has non-specific symptoms and may not be detected until an advanced stage

- Ovarian cancer accounts for an estimated 239,000 new cases and 152,000 deaths worldwide annually\(^1\)
- The estimated lifetime risk for a woman developing ovarian cancer is 1 in 75, and her chance of dying from the disease is 1 in 100\(^1\)
- The disease typically presents at late stage when the 5-year relative survival rate is only 29\(^1\)

**Age-standardised incidence and mortality rates worldwide in 2012: women\(^2\)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
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<tr>
<td>Cervix uteri</td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td></td>
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<tr>
<td>Corpus uteri</td>
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<tr>
<td>Stomach</td>
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<tr>
<td>Ovarian</td>
<td></td>
<td></td>
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<tr>
<td>Thyroid</td>
<td></td>
<td></td>
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<tr>
<td>Liver</td>
<td></td>
<td></td>
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<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ASR (W) rate per 100,000**
Patients often receive multiple treatment lines, with decreasing periods of remission between regimens\textsuperscript{1,2}

There is a need for therapies that can extend the time between lines of cytotoxic chemotherapy

<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>18.2 months</td>
</tr>
<tr>
<td>Second line</td>
<td>10.2 months</td>
</tr>
<tr>
<td>Third line</td>
<td>6.4 months</td>
</tr>
<tr>
<td>Fourth line</td>
<td>5.6 months</td>
</tr>
<tr>
<td>Fifth line</td>
<td>4.4 months</td>
</tr>
</tbody>
</table>

Characterisation of the second to sixth line therapy and its effects on survival was carried out, based on data of n=1620 patients with advanced epithelial ovarian cancer from three large randomised phase III trials investigating primary therapy with different combination chemotherapy regimens\textsuperscript{2}
Epithelial ovarian cancer subtypes display distinct genetic mutations\(^1\)

High-grade serous ovarian cancer encompasses \(~60\%\) of all epithelial ovarian cancers\(^1\)

Histologic subtypes of epithelial ovarian cancers and their associated mutations and molecular aberrations\(^1,2\)

- **High-grade serous**
  - TP53, BRCA1/2, NF1, FAT3, CSMD3, GABRA6, RB1, CDK12
  - \(\sim 60\%\)

- **Low-grade serous**
  - BRAF, KRAS, PIK3CA, PTEN
  - \(\sim 5\%\)

- **Endometrioid**
  - ARID1A, BRAF, CTNNB1, PIK3CA, PTEN
  - \(\sim 25\%\)

- **Clear cell**
  - ARID1A, KRAS, PIK3CA, PTEN
  - \(\sim 4\%\)

- **Mucinous**
  - BRAF, KRAS, HER2
  - \(\sim 4\%\)

- **Other**
  - 2\%

Histologic subtypes of epithelial ovarian cancers and their associated mutations and molecular aberrations\(^1,2\)
High-grade serous ovarian cancer is the most common form of epithelial ovarian cancer\textsuperscript{1,2}

HGS OC is often diagnosed at an advanced stage\textsuperscript{1}

- HGS OC may have a fallopian tube epithelium origin, with a serous tubal \textit{in situ} carcinoma precursor\textsuperscript{1}

- Recent evidence suggests that the dissemination of presumed pluripotent stem cells across the peritoneal area may result in multiple foci independently becoming cancerous\textsuperscript{3}
HGS OC is genotypically unstable and can be classified by molecular subgroups

Approximately half of HGS OC harbour defects in homologous recombination

HR = homologous recombination
Summary

Epithelial OC is a collection of varied histologic and molecularly different malignancies, many of which may not derive from a true ovarian anatomic precursor.

- Epithelial ovarian cancer subtypes display distinct genetic mutations.

High-grade serous ovarian cancer encompasses ~60% of all epithelial ovarian cancers.

- Of these, ~50% harbour defects in homologous recombination repair.

Ovarian cancer, and in particular, high grade serous ovarian cancer is commonly associated with genomic instability.
PARP inhibitors – therapeutic paradigm in ovarian cancer

Biomarkers for PARP sensitivity
Lynparza tablet and capsule indications for ovarian cancer

• Lynparza tablets are indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy¹
  – Tablets are available in 100 and 150 mg¹

• Lynparza capsules are indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy²
  – Each hard capsule contains 50mg of olaparib²

• Lynparza tablets (100mg and 150mg) should not be substituted for Lynparza capsules (50mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Therefore, the specific dose recommendations for each formulation should be followed.¹

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¹ Lynparza 100mg and 150mg film-coated tablets Summary of Product Characteristics 2018;
² Lynparza 50 mg hard capsules Summary of Product Characteristics 2018
Lynparza targets PARP causing a synthetic lethal interaction in cancers with homologous recombination deficiency\textsuperscript{1}

PARP is required to repair single strand DNA breaks through base excision repair\textsuperscript{2,3}

PARP enzyme required to repair single strand DNA breaks

Single strand break

Normal cell

Repair by base excision repair
Lynparza targets PARP causing a synthetic lethal interaction in cancers with homologous recombination deficiency\(^1\)

Homologous recombination repairs double strand DNA breaks in normal cells\(^2-3\)
Lynparza targets PARP causing a synthetic lethal interaction in cancers with homologous recombination deficiency\(^1\)

In tumour cells with defective HRR, accumulation of cytotoxic DSBs lead to cell death\(^2\)-\(^3\)
Biomarkers for PARP inhibitors sensitivity include *BRCA*m, HRD and platinum-sensitivity

PARP inhibitor sensitivity has shown to be increased in patients with a *BRCA*m or HRD, however patients without these biomarkers who are platinum-sensitive also respond to PARP inhibition$^{1-3}$

### Laboratory biomarkers$^{4,5}$

**BRCA mutations:** ~20% of high-grade serous cancers have a *BRCA* mutation

**Homologous recombination deficiency (HRD):** ~50% of high-grade serous cancers have HRD

### Clinical biomarkers$^{4,6,7}$

**Degree of platinum sensitivity**
Clinical selection factors are the most effective tools to identify relapsed HG SOC patients who may benefit from PARP inhibitor treatment.

- While evaluation of diagnostic approaches continues, platinum sensitivity and response to platinum are currently the most appropriate tools to inform PARP inhibitor response\textsuperscript{1,2}.

- Absence of a fully functional HRR pathway is known to be associated with platinum sensitivity in ovarian cancer\textsuperscript{3}.

- Therefore, while evaluation of diagnostic approaches continues, platinum sensitivity and response to platinum are currently the most appropriate tools to inform PARP inhibitor response\textsuperscript{1,2}. 
PARP inhibitors are specifically designed to target tumour cells with homologous recombination deficiency (HRD)\(^1\)
- They bind to and trap PARP onto DNA at the sites of single strand breaks, which results in the generation of a double strand breaks (DSBs)\(^1\)
- In HRD cancer cells, accumulation of cytotoxic DSBs leads to cell death\(^1\)

Several biomarkers can be used to identify PARP inhibitor sensitivity
- Clinical biomarkers – sensitivity to platinum based chemotherapy\(^2,3\)
- Laboratory markers – mutations in HRR genes (e.g. BRCA\(^m\))\(^2,4\)

Platinum sensitive high-grade epithelial ovarian cancer patients clinically enriched for underlying HRD are therefore most likely to achieve clinical benefit from PARP inhibitors\(^5,6,7\)
Clinical evidence for Lynparza
There have been two large, randomised trials of maintenance Lynparza in PSR ovarian cancer\textsuperscript{1,2}

Together these trials provide evidence for maintenance Lynparza in platinum sensitive relapsed patients

**Study 19 (n=265)**

**Phase II study\textsuperscript{1}**
- Recurrent ovarian cancer after two prior lines of platinum therapy
- Maintenance in patients achieving a CR/PR on platinum therapy
- 1:1 randomisation to Lynparza 400mg bid (capsule) or placebo
- Primary endpoint investigator-assessed PFS in overall population (PSR OC)

**Solo 2 (n=295)**

**Phase III study\textsuperscript{2}**
- Recurrent $BRCA_m$ ovarian cancer after two prior lines of platinum therapy
- Maintenance in patients achieving a CR/PR on platinum therapy
- 2:1 randomisation to Lynparza 300mg bid (tablet) or placebo
- Primary endpoint investigator-assessed PFS ($BRCA_m$ PSR OC)

Study 19: The first pivotal trial of a PARP inhibitor as maintenance treatment in PSR ovarian cancer\(^1,2\)

Study 19 was a Phase II double blind, randomised, placebo controlled trial\(^1,2\)

Patients
- Recurrent, platinum-sensitive high-grade serous ovarian* cancer
- Completion of ≥2 platinum-based chemotherapy regimens
- Objective response (RECIST) or CA-125 response (GCIG criteria) to most recent regimen
- CA-125 below ULN, or stable, at study entry

NOTE: BRCA1/2 mutation status was recorded if available, but was NOT required for study participation and was not a stratification factor

Randomise 1:1
\(N=265\)

Stratification by:
- Interval between disease progression and completion of penultimate platinum-based regimen (6–12 or >12 months)
- Objective response to their most recent regimen (CR or PR)
- Ancestry (Jewish or non-Jewish)

Lynparza
\(po\) 400 mg bid\(^\dagger\)
\(n=136\)

Placebo
\(n=129\)

Primary endpoint
- PFS

Secondary endpoints
- OS
- Best overall response
- Response rate
- Disease control rate
- Duration of response
- Change in tumour size
- CA-125 response (GCIG criteria)
- TTP by CA-125 or RECIST
- Safety
- QoL

*or fallopian tube or primary peritoneal; †Capsule formulation

RECIST=Response Evaluation Criteria in Solid Tumours; GCIG=Gynecological Cancer Intergroup; ULN=upper limit of normal; CR=complete response; PR=partial response; \(po=orally; bid=twice daily; PFS=progression-free survival; OS=overall survival; TTP=time to progression; QoL=quality of life
Study 19: Maintenance treatment with Lynparza extended investigator-assessed PFS in platinum sensitive relapsed OC (primary endpoint)\(^1,2\)

A significant increase in progression-free survival was seen with Lynparza vs placebo\(^1\)

![Graph showing progression-free survival](image)

<table>
<thead>
<tr>
<th></th>
<th>Lynparza</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, N [%]</td>
<td>60/136 [44.1]</td>
<td>94/129 [72.9]</td>
</tr>
<tr>
<td>Median PFS months (95% CI)</td>
<td>8.4 (7.4-11.5)</td>
<td>4.8 (4.0-5.5)</td>
</tr>
<tr>
<td>HR</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>95% CI: 0.25, 0.49; P&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^2\) Analysis was performed after 154 progression events had occurred (in 58% of patients)

HR=hazard ratio; CI=confidence interval

- Figure adapted from Ledermann J, et al. Lancet Oncol. 2014;15:852–861
- 2. Lynparza 100mg and 150mg film-coated tablets Summary of Product Characteristics 2018
Study 19: PFS was extended regardless of $BRCAm$ status\(^1\)

The greatest benefit was observed in patients with $BRCAm$\(^1\)

### Study 19: progression-free survival in $BRCAm$ patients\(^*\)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Lynparza (n=74)</th>
<th>Placebo (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>11.2</td>
<td>4.3</td>
</tr>
<tr>
<td>HR (= 0.18) (95% CI = 0.10-0.31) (p&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pre-specified, p-values not adjusted for multiplicity. DCO: June 2010; Median overall PFS FU: 5.6 months\(^1\)

### Study 19: progression-free survival in non-$BRCAm$ patients\(^*\)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Lynparza (n=57)</th>
<th>Placebo (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>HR (= 0.54) (95% CI = 0.34-0.85) (p=0.0075)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pre-specified, p-values not adjusted for multiplicity. DCO: June 2010; Median overall PFS FU: 5.6 months\(^1\)
Study 19: The PFS result is supported by a range of long term analyses (follow up >6 years)\(^1,2\)

With over 6 years of follow-up, mature data from a range of analyses are consistent with the primary PFS, demonstrating a clinically meaningful long term clinical benefit regardless of \(\text{BRCA}\text{m}\) status\(^1-3\)

- **Primary PFS\(^3\)**
  - Median FU: 5.6 months\(^4\)

- **TFST/TSST analysis\(^1\)**
  - Median FU: TFST: 70.8 months, TSST: 70.5 months\(^1\)

- **Final OS analysis\(^2\)**
  - Median FU: 78.0 months\(^2\)

FSI=first subject in; LSI=last subject in; DCO=data cut-off; FU=follow-up; TFST = time to first subsequent treatment; TSST = time to second subsequent treatment

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Study 19: Delay in time to first subsequent therapy in the PSR population of 6.7 months*1

In the overall population the time to first subsequent therapy (TFST) was increased in the Lynparza treated arm compared to placebo (HR 0.39, 95% CI 0.29-0.51, p<0.0001)1*

*There was no strategy for multiple testing for the exploratory TFST analysis
Study 19: TSST shows the benefit of Lynparza vs. placebo remains beyond the treatment period\(^1\)

Patients receiving Lynparza had a 48% reduction in the risk of second progression or death vs. placebo (HR=0.52, 95% CI: 0.39-0.68)\(^1\)

\[\text{HR}=0.52, \ 95\% \ CI: 0.39-0.68; \ P<0.0001^*\]

<table>
<thead>
<tr>
<th></th>
<th>Lynparza</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, N [%]</td>
<td>103/136 [76]</td>
<td>119/128 [93]</td>
</tr>
<tr>
<td>Median TSST months (95% CI)</td>
<td>19.1 (16.5-22.0)</td>
<td>14.8 (14.0-17.2)</td>
</tr>
</tbody>
</table>

*Exploratory analysis
DCO: September 2015; Median FU TSST: 70.5 months\(^1\)

There was no strategy for multiple testing for the exploratory TSST analysis

Study 19: Lynparza suggested a 27% reduction in the risk of death compared to placebo in the overall population at the final DCO\(^1-^3\)

<table>
<thead>
<tr>
<th>Lynparza 400 mg bd</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>136</td>
</tr>
<tr>
<td>Events (%)</td>
<td>98 (72.1)</td>
</tr>
<tr>
<td>Median</td>
<td>29.8</td>
</tr>
</tbody>
</table>

HR = 0.73  
95% CI (0.55, 0.95)  
Nominal p=0.02138

13% of placebo-receiving patients received post-discontinuation PARP inhibitor treatment in other studies

Median OS follow-up: 78.0 months
To maintain statistical rigour the requirement for declaring significant OS benefit in the full analysis set at this analysis is p<0.0095, which was not met. OS was a secondary endpoint in the clinical trial.
Study 19: More than 10% of PSR OC patients remain on Lynparza for ≥6 years$^{1,2}$

11% of patients remained on treatment for ≥6 years with similar numbers of both BRCAm and non-BRCA patients receiving long-term treatment$^1$

<table>
<thead>
<tr>
<th>Time on Lynparza (years)</th>
<th>BRCAm subgroup (n=74)</th>
<th>non-BRCAm subgroup (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>46%</td>
<td>33%</td>
</tr>
<tr>
<td>≥2</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>≥3</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>≥4</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>≥5</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td>≥6</td>
<td>14%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Subgroups were defined prior to exploratory biomarker analyses being performed; patients with no known BRCAm or a variant of unknown significance were classified as non-BRCA, and one patient with no known BRCAm who received Lynparza treatment for ≥6 years was found to have a somatic BRCAm in subsequent Myriad tumor testing. DCO: May 2016
SOLO2: A Phase 3 trial of Lynparza tablets in BRCAm PSR OC\textsuperscript{1,2}

Platinum-sensitive high-grade serous ovarian* or high-grade endometrioid cancer having relapsed following ≥2 prior lines of platinum-based chemotherapy

Clinical CR/PR following completion of last platinum-based chemotherapy (min 4 cycles)

ECOG PS 0–1

Documented BRCAm, or patient willing to consent to testing (only those with deleterious or suspected deleterious germline mutations will be randomised)

Randomise within 8 weeks of last chemotherapy dose

Randomise 2:1 N=295

Lynparza (n=196) 300mg** po bid

Placebo (n=99)

Stratification by response to previous platinum-based chemotherapy and time to disease progression in penultimate platinum-based chemotherapy

Key secondary endpoints

PFS2

OS

Primary endpoint

PFS

RECIST 1.1 Investigator assessed

Investigator assessed

*Includes patients with primary peritoneal and/or fallopian tube cancer; **Tablet formulation
SOLO2: designed to provide additional evidence for Lynparza in patients with *BRCA*m PSR OC\textsuperscript{1,2}

- SOLO2 reported data on the new tablet formulation of Lynparza; this is different from Study 19 where a capsule formulation was used\textsuperscript{1-3}

- The tablet formulation used in SOLO2 was chosen based on data from phase 1 of Study 24 \textsuperscript{4}

- The recommended tablet dose was 300 mg administered as 2 x 150 mg tablets, twice daily\textsuperscript{4}
SOLO2: Significant PFS benefit in *BRCA*m PSR OC (primary endpoint)*1,2*

Risk of progression or death during the study was reduced by 70% for patients taking Lynparza compared to placebo*1*

Investigator-assessed PFS at 63% maturity. Median follow-up for PFS was 22.1 months in the Lynparza group and 22.2 months for placebo
Full assessment set n=295, Data cutoff: 19 September 2016
SOLO2: BICR analysis of PFS suggests more than 2 year benefit with Lynparza vs. placebo\(^1,2\)

- **BICR-assessed PFS at 51% maturity**
- **Full assessment set n=295, Data cutoff: 19 September 2016**

### Kaplan-Meier curve

- **Proportion of patients progression free**
- **Time from randomisation (months)**

<table>
<thead>
<tr>
<th></th>
<th>Lynparza 300 mg bid</th>
<th>Placebo bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>81/196</td>
<td>70/99</td>
</tr>
<tr>
<td>(41.3%)</td>
<td>(70.7%)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>30.2 m</td>
<td>5.5 m</td>
</tr>
<tr>
<td>HR</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.18,0.35)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

### Table: Proportion of patients progression free at 36 months

<table>
<thead>
<tr>
<th>Time from randomisation (months)</th>
<th>Lynparza 300 mg bid</th>
<th>Placebo bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
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<td>98</td>
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<td>12</td>
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<td>18</td>
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<td>33</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>36</td>
<td>36</td>
<td>100</td>
</tr>
</tbody>
</table>
SOLO2: Over half of patients were progression free in the Lynparza arm at 18 months compared to approximately 16% in the placebo arm¹

*Investigator-assessed PFS (calculated using KM techniques)

Full assessment set n=295, Data cutoff: 19 September 2016

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¹Investigator-assessed PFS (calculated using KM techniques)

Full assessment set n=295, Data cutoff: 19 September 2016
SOLO2: Secondary efficacy endpoints demonstrated continued benefit beyond progression with Lynparza treatment compared with placebo\textsuperscript{1,2}

- **Time to 1\textsuperscript{st} subsequent treatment (TFST)**
  - Lynparza: 27.9 months
  - Placebo: 7.1 months
  - HR 0.28, 95% CI 0.21 to 0.38, p<0.0001

- **Time to 2\textsuperscript{nd} progression (PFS2)**
  - Median not reached in Lynparza group
  - Lynparza: 18.4 months
  - Placebo: 7.1 months
  - HR 0.50, 95% CI 0.34 to 0.72, p=0.0002

- **Time to 2\textsuperscript{nd} subsequent treatment (TSST)**
  - Median not reached in Lynparza group
  - Lynparza: 18.2 months
  - Placebo: 7.1 months
  - HR 0.37, 95% CI 0.26 to 0.53, p<0.0001

- **Overall Survival (OS)**
  - Data are immature

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**BRCA in Ovarian Cancer**

**Leading Operational Guidelines**

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\textsuperscript{1} Data for Survival endpoints are immature. 

\textsuperscript{2} No events occurred beyond 18 months in either treatment group.
### Lynparza has a well-tolerated safety profile

#### Adverse reactions (Pooled data from 1248 patients treated with Lynparza monotherapy)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency of All CTCAE grades</th>
<th>Frequency of CTCAE grade 3 and above</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Only include preferred terms (PTs) of <em>anaemia</em>, <em>haemoglobin decreased</em>, <em>red blood cell count decreased</em>, <em>erythropenia</em> and <em>haematocrit decreased</em>; <em>neutropenia</em> includes PTs of <em>neutropenia</em>, <em>granulocytopenia</em>, <em>granulocyte count decreased</em> and <em>neutrophil count decreased</em>, <em>febrile neutropenia</em>, <em>neutropenic infection</em> and <em>neutropenic sepsis</em>; <em>thrombocytopenia</em> includes PTs of <em>thrombocytopenia</em>, <em>platelet count decreased</em>, <em>platelet production decreased</em> and <em>plateletcrit decreased</em>; <em>leukopenia</em> includes PTs of <em>leukopenia</em> and <em>white blood cell count decreased</em>; <em>cough</em> includes PTs of <em>cough</em> and <em>productive cough</em>; <em>rash</em> includes PTs of <em>rash</em>, <em>erythematous</em>, <em>generalised</em>, <em>macular</em>, <em>maculopapular</em>, <em>papular</em>, <em>pruritic</em>, <em>exfoliative</em> and <em>generalised erythema</em>; <em>hypersensitivity</em> includes PTs of <em>hypersensitivity</em> and <em>drug hypersensitivity</em>; <em>dermatitis</em> includes PTs of <em>dermatitis</em>, <em>dermatitis allergic</em> and <em>dermatitis exfoliative</em>.</td>
<td></td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Very common Anaemia*³</td>
<td>Very common Anaemia*³</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Very common Decreased appetite</td>
<td>Uncommon Decreased appetite</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Common Dizziness, Headache, Dysgeusia</td>
<td>Uncommon Dizziness, Headache</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Very common Cough*³</td>
<td>Uncommon Cough*³</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Very common Vomiting, Diarrhoea, Nausea, Dyspepsia</td>
<td>Common Vomiting, Diarrhoea, Nausea</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Very common Fatigue (including asthenia)</td>
<td>Common Fatigue (including asthenia)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Common Increase in blood creatinine</td>
<td>Uncommon Increase in blood creatinine</td>
</tr>
</tbody>
</table>

*Represents the incidence of laboratory findings of elevations in mean corpuscular volume from baseline to above the upper limit of normal (ULN), not of reported adverse reactions.
Dosing and monitoring for Lynparza capsules and tablets in PSR OC

<table>
<thead>
<tr>
<th></th>
<th>Lynparza capsules¹</th>
<th>Lynparza tablets²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>8 x 50 mg capsules bd</td>
<td>2 x 150 mg tablets bd</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td>No. Patients should take Lynparza at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards.</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CBCs</strong></td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Blood pressure monitoring</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Store in a refrigerator (2°C - 8°C). Do not freeze. Any capsules that have been frozen must be discarded. Can be stored for up to 3 months below 30°C. The capsules must be discarded after this period.</td>
<td>Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.</td>
</tr>
</tbody>
</table>

Lynparza tablets (100 mg and 150 mg) should not be substituted for Lynparza capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Therefore, the specific dose recommendations for each formulation should be followed.²
Study 19 and SOLO2: The majority of patients receiving maintenance Lynparza were able to maintain full dosing throughout their treatment\textsuperscript{1,2}

Both the capsule and tablet formulations have been shown to have similar AE profiles. An increased risk of \textsuperscript{>}$\text{grade 3}$ anaemia was observed with tablets compared to capsules. The majority of AEs are low grade and manageable through supportive treatment and dose adjustments\textsuperscript{1,2}

<table>
<thead>
<tr>
<th></th>
<th>SOLO2 (PSR BRCAm)\textsuperscript{1}</th>
<th>Study 19 (PSR)\textsuperscript{2,3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynparza (n=195)</td>
<td>Placebo (n=99)</td>
<td>Lynparza (n=136)</td>
</tr>
<tr>
<td>Dose interruption, %</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>Dose reduction, %</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Treatment discontinuation, %</td>
<td>11</td>
<td>2</td>
</tr>
</tbody>
</table>
Study 19 and SOLO2: No detrimental effect on health-related quality of life (HRQoL) was observed compared to placebo\textsuperscript{1-3}

Active maintenance treatment with Lynparza was not associated with HRQoL deterioration compared to placebo

- HRQoL, as measured by the Trial Outcome Index, remained consistent over time and similar for Lynparza and placebo in both Study 19 and SOLO2\textsuperscript{1-3}

- Additionally, in SOLO2, further patient-centred analysis (QAPFS and TWiST) were carried out. Significant benefits were seen in the Lynparza treatment group compared to placebo\textsuperscript{1}
  - QAPFS showed a significant 6.68 month benefit to Lynparza treated patients\textsuperscript{1}
  - TWiST showed a significant 6.29 month benefit to Lynparza treated patients\textsuperscript{1}

HRQoL=health-related quality of life; QAPFS=quality adjusted progression-free survival; TWiST=time without symptoms of disease and toxicity

\textbullet\ \ 1. Friedlander M et al. \textit{J Clin Oncol} 2017;35(suppl):abstr 5507 (and associated presentation);
\textbullet\ \ 3. Ledermann J et al. \textit{Br J Cancer}. 2016;155(11):1313–1320
Summary: Lynparza in platinum-sensitive relapsed ovarian cancer

- There are two pivotal studies of Lynparza maintenance therapy in relapsed, platinum-sensitive ovarian cancer\(^1,2\):

**Study 19**
- Lynparza **capsules** significantly prolonged PFS compared with placebo (HR 0.35; 95% CI 0.25 to 0.49; \(p<0.001\)), regardless of \(BRCA\)m status\(^1,3\)
- Approximately 20% of patients still receive Lynparza treatment at 3 years
- **Lynparza is the only PARP inhibitor with over 10% of patients remaining on treatment after 5 years**\(^4,5\)

**Solo 2**
- Lynparza **tablets** significantly prolonged PFS in a \(BRCA\)m population compared with placebo (HR 0.30; 95% CI 0.22 to 0.41; \(p<0.0001\)), with BICR sensitivity analysis suggesting this benefit could be >2 years\(^2\)

**Long-term safety and tolerability profile**
- In Study 19 and SOLO2 the majority of patients receiving maintenance Lynparza were able to maintain full dosing throughout their treatment\(^2,4\)
- In both studies, adverse events reported were generally mild to moderate, and manageable with supportive treatment and dose modifications\(^1-6\)
References

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