

**NIHR Innovation Observatory  
Evidence Briefing: June 2017****Olaparib (Lynparza) tablets for recurrent platinum-sensitive BRCA-mutated ovarian cancer – maintenance therapy**

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**LAY SUMMARY**

Cancer of the ovaries is the sixth most common cancer in women. Some women are born with an error in a gene called BRCA, and have an increased chance of developing breast and ovarian cancer. Patients with ovarian cancer are often diagnosed at a late stage and despite initial treatment success, the disease often returns. In 'platinum-sensitive' ovarian cancer, the cancer has come back (relapsed) more than six months after the last dose of platinum-based chemotherapy (the initial treatment).

Olaparib is a drug that kills cancer cells, and is already recommended by NICE as an option for patients with this type of ovarian cancer (BRCA-mutated, platinum-sensitive) who have had three or more courses of platinum-based chemotherapy. The drug has now been trialled in tablet form for patients who have received at least two prior lines of platinum-based chemotherapy. This new tablet formulation of olaparib could ease the treatment burden for patients – reducing the number of pills taken from 16 capsules to four tablets per day.

*This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Ovarian, peritoneal or fallopian tube cancer, with germline BRCA-mutations; recurrent, platinum-sensitive cancer – maintenance monotherapy, patients have completed  $\geq 2$  lines of platinum therapy

## TECHNOLOGY

### DESCRIPTION

Olaparib (Lynparza; AZD-2281; KU-0059436) is a first-in-class potent inhibitor of human poly (ADP-ribose) polymerase (PARP) enzymes. PARP are a family of proteins involved in cellular processes such as DNA repair, genomic stability, and programmed cell death. Olaparib selectively binds to and inhibits PARP, inhibiting PARP-mediated repair of single strand DNA breaks. PARP inhibition enhances the cytotoxicity of DNA-damaging agents and reverses the tumour cells' resistance to chemotherapy. This can result in disruption of cellular homeostasis and cell death.<sup>1</sup>

The capsule formulation of olaparib is licensed in the EU for the maintenance treatment of platinum-sensitive relapsed BRCA-mutated high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who have responded to platinum-based chemotherapy.<sup>1 2</sup> It is taken orally and the recommended dose is 400mg twice daily (16 x 50mg capsules per day).

NICE recommends olaparib capsules as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum based chemotherapy only if they have had three or more courses of platinum based chemotherapy. NICE also required that the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.<sup>3</sup> Despite its EMA marketing authorisation, NICE has so far not recommended second-line treatment with olaparib.<sup>2</sup>

The FDA has approved olaparib capsules as fourth line monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.<sup>1</sup> The most common ( $\geq 10\%$ ) adverse effects associated with olaparib capsule monotherapy include: nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, anaemia, neutropaenia, lymphopaenia, mean corpuscular volume elevation, and increase in creatinine.<sup>4</sup>

Due to the high pill burden associated with olaparib capsules, a new tablet formulation of olaparib has been tested in recent clinical trials. The tablet formulation is not directly bioequivalent to the olaparib capsule formulation.<sup>5</sup> The dose of olaparib tablets in clinical trials is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg (4 tablets).<sup>1</sup>

Olaparib tablets are not yet approved for any use in any indication.

Olaparib is also in phase III clinical trials for breast cancer, pancreatic cancer, and prostate cancer, and in phase II trials for lung cancer, and head and neck squamous cell carcinoma.<sup>1</sup>

## INNOVATION and/or ADVANTAGES

Women with recurrent or persistent ovarian cancer have high recurrence rates within 12 to 24 months following the completion of a platinum-containing treatment regimen. There remains a high unmet need for improved treatment options for this population.

Olaparib and other PARP inhibitors are considered to represent a significant advance in the treatment of ovarian cancer.<sup>2</sup> The new tablet formulation of olaparib may reduce treatment burden from 16 capsules to four tablets a day.

While a number of PARP inhibitors are entering the market, many unanswered questions still remain, e.g. related to when in the treatment pathway PARP inhibitors should be used and whether they are best used as maintenance treatment after chemotherapy, as monotherapy for active treatment, or in combination with chemotherapy.<sup>6</sup>

## DEVELOPER

AstraZeneca

## AVAILABILITY, LAUNCH or MARKETING

AstraZeneca announced in March 2017 that the FDA had accepted its New Drug Application (NDA) for olaparib tablets (300mg twice daily) for use in platinum-sensitive, relapsed ovarian cancer patients in the maintenance setting. The FDA has also granted priority review status with a Prescription Drug User Fee Act (PDUFA) set for third quarter 2017.<sup>1</sup>

## PATIENT GROUP

### BACKGROUND

Ovarian cancer is a common gynaecological cancer, encompassing a range of tumours arising from different types of ovarian tissue. The most common type of ovarian cancer is epithelial, which often spreads to other surfaces within the abdominal cavity, including the fallopian tube and peritoneal cavity.<sup>7</sup> 90% of ovarian tumours are epithelial, while primary peritoneal and fallopian tube cancers are both rare malignancies; all three cancers are managed in a similar way.<sup>8,9</sup> Symptoms of ovarian cancer are often non-specific, such as persistent pelvic and abdominal pain, bloating, and bleeding. Most women are consequently diagnosed at an advanced stage of the disease.<sup>7</sup>

On average, women have about a 2% chance of developing ovarian cancer in their lifetime, but in women who have a faulty BRCA1 or BRCA2 gene, this increases to between 40 to 60% or between 10 to 30%, respectively. The risk of developing the cancer starts to increase from around the age of 40 years for BRCA1 carriers and in the mid-40s for women who are BRCA2 carriers.<sup>10</sup>

Women with ovarian cancer often experience persistence or recurrence despite an initial response to platinum-based chemotherapy (first line treatment). Between 55% to 75% of women relapse within two years of completing chemotherapy. Recurrent ovarian cancer may be categorised as follows:

- **platinum-sensitive** disease: responds to first line platinum-based therapy but relapses after >6 months;
- **partially platinum-sensitive** disease: relapses between 6 and 12 months;
- **fully platinum-sensitive** disease: relapses after 12 months or more;
- **platinum-resistant** disease: relapses within 6 months of completion of initial platinum-based chemotherapy;
- **platinum-refractory** disease: does not respond to initial platinum-based chemotherapy.<sup>7</sup>

For patients with platinum-resistant or refractory disease, treatment generally focuses on quality of life and control of symptoms as this population has a poor prognosis and a short expected overall survival.<sup>11</sup>

The cause of ovarian cancer is often unknown, but besides inherited genetic mutations (such as BRCA1/2), recognised risk factors include age, prior breast cancer, fertility treatment, smoking, and being overweight.<sup>12</sup>

## CLINICAL NEED and BURDEN OF DISEASE

Ovarian cancer is the sixth most common cancer in women.<sup>13</sup> 6,198 cases of ovarian cancer were registered in England in 2015.<sup>14</sup> Over 80% of cases of ovarian cancer are diagnosed in women aged over 50 years.<sup>7</sup> Family history is associated with early-onset disease.<sup>15</sup>

The five-year survival rate for ovarian cancer is 43%.<sup>7</sup> Survival is dependent on the stage of cancer at diagnosis, success of surgery in removing the tumour, patient's performance status and age – 35% of women in England and Wales will survive their ovarian cancer for 10 years or more.<sup>16</sup> Recurrence of the cancer is however associated with poorer prognosis, and has a significant impact on emotional and physical well-being, often resulting in the patient's inability to work and requirement for ongoing support.<sup>7</sup>

In 2015-16, there were 35,935 admissions for malignant neoplasm of ovary (ICD-10 code C56), resulting in 57,016 bed days and 38,154 finished consultant episodes in England.<sup>17</sup>

## PATIENT PATHWAY

## RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal in development. Ovarian cancer (platinum sensitive) – cediranib (ID790). **Suspended** October 2016.
- NICE technology appraisal. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). April 2016.

- NICE technology appraisal. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). January 2016.
- NICE technology appraisal. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). May 2013.
- NICE technology appraisal. Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer (TA285). May 2013.
- NICE technology appraisal. Trabectedin for the treatment of relapsed ovarian cancer (TA222). April 2011.
- NICE technology appraisal. Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. Review of Technology appraisal guidance 28, 45 and 55 (TA91). May 2005.
- NICE technology appraisal. Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). January 2003.
- NICE guideline. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE quality standard. Quality standard for ovarian cancer (QS18). May 2012.
- NICE advice. Ovarian cancer (advanced): bevacizumab 7.5mg/kg in combination with paclitaxel and carboplatin for first-line treatment (ESUOM21). October 2013.

## NHS ENGLAND and POLICY GUIDANCE

- NHS England. NHS Standard Contract for Complex Gynaecology - Specialist Gynaecological Cancers. E10/S/f. 2013.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

## OTHER GUIDANCE

- Morgan, RJ, Armstrong, DK, Alvarez, RD, et al. Ovarian cancer, version 1.2016, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, 2016; 14 (9): 1134-1163.

## CURRENT TREATMENT OPTIONS

Treatment options for recurrent ovarian cancer are currently very limited. The most recent NICE technology appraisal guidance recommends pegylated liposomal doxorubicin (PLD) or paclitaxel (as monotherapy or in combination with platinum therapy) as options for treating recurrent ovarian cancer.<sup>7</sup> ESMO guidelines state that the selection of therapy should be based on toxicity, patient's clinical situation, and the convenience of administration. Cytoreductive surgery in relapsed epithelial ovarian cancer remains controversial due to lack of evidence for this approach in prospective trials.

Olaparib is the only PARP inhibitor approved for use in any indication in Europe. In the USA, olaparib had no direct competition in the ovarian cancer market for two years, but in March 2017 FDA approved niraparib (Zejula), for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.<sup>6 18</sup> Another PARP inhibitor in development is rucaparib (Rubraca). Global Data estimates that four approved PARP inhibitors will be available by 2025.<sup>6</sup>

## EFFICACY and SAFETY

<b>Trial</b>	<b>SOLO-2, NCT01874353, ENGOT-Ov21; olaparib (Lynparza) tablet formulation vs. placebo as maintenance monotherapy, phase III</b>
<b>Sponsor</b>	AstraZeneca, European Network of Gynaecological Oncology Trial Groups
<b>Status</b>	Ongoing, not recruiting
<b>Source of Information</b>	Trial registry, <sup>19</sup> conference presentation, <sup>20</sup> Global Data, <sup>1</sup> press releases <sup>21 22</sup>
<b>Location</b>	US, EU (incl UK), Canada, China, and other countries
<b>Design</b>	Randomised, double-blind, placebo-controlled study
<b>Participants</b>	N=295, olaparib n=196, placebo n=99 (ClinicalTrials.gov: n=729); females ≥18 years of age; histologically diagnosed relapsed high grade serous ovarian cancer (including primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer; documented mutation in BRCA1 or BRCA2; must have received at least 2 previous lines of platinum-containing therapy prior to randomisation and defined as platinum sensitive after the most recent treatment.
<b>Schedule</b>	300mg olaparib or placebo tablets taken orally twice daily until objective radiological disease progression as per RECIST guidelines as assessed by the investigator (or as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria). Dose reduction to 250mg and subsequently 200mg is permitted following confirmation of toxicity.
<b>Follow-up</b>	Median follow-up was 22.1 months in the olaparib group and 22.2 months for placebo.
<b>Primary Outcomes</b>	Progression Free Survival (PFS) by investigator assessment (ClinicalTrials.gov: Progression Free Survival (PFS) by central review of RECIST data)
<b>Secondary Outcomes</b>	Efficacy in patients following platinum based chemotherapy by assessment of overall survival; Efficacy in patients following platinum-based chemotherapy by assessment of time to earliest progression by RECIST or Cancer Antigen (CA-125) or death; Efficacy in patients following platinum-based chemotherapy by assessment of time from randomisation to second progression; Change from baseline in Health-Related Quality of Life (HRQoL); Efficacy in patients with a deleterious or suspected deleterious variant in either of the BRCA genes by assessment of PFS (full list available in trial registry entry)
<b>Key Results</b>	AstraZeneca announced in March 2017 that results from SOLO-2 demonstrated a significant improvement in progression-free survival (PFS) compared with placebo in the maintenance setting. The trial met its primary endpoint of investigator assessed PFS (HR 0.30, 95% CI: 0.22 to 0.41, P≤0.0001, median 19.1 months vs 5.5 months). PFS as measured by Blinded Independent

	Central Review (BICR) evaluation demonstrated a median PFS of 30.2 months vs 5.5 months for placebo, representing an improvement of 24.7 months (HR 0.25, 95% CI: 0.18 to 0.35, P≤0.0001). Additionally, a statistically-significant benefit in time to second progression or death (PFS2) was also seen in patients treated with olaparib tablets (HR 0.50, 95% CI: 0.34 to 0.72, P=0.0002, median not reached vs 18.4 months) compared with placebo, as well as improvements in other key secondary endpoints.
<b>Adverse effects (AEs)</b>	<p>The safety profile for patients treated with olaparib tablets during the SOLO-2 trial was generally consistent with those observed with the currently approved capsule formulation. Grade ≥3 adverse events were reported in 36.9% of patients treated with olaparib, and in 18.2% of patients who received placebo.</p> <p>The most common non-haematological AEs reported at a frequency of ≥20% in the olaparib arm versus placebo were nausea (75.9% vs 33.3%), fatigue/asthenia (65.6% vs 39.4%), and vomiting (37.4% vs 19.2%). Grade ≥3 non-haematological AEs reported at a frequency of ≥2.5% in the LYNPARZA arm versus placebo were fatigue/asthenia (4.1% vs 2.0%), vomiting (2.6 % vs 1.0%), abdominal pain (2.6% vs 3.0%), nausea (2.6% vs 0.0%), diarrhoea (1.0% vs 0.0%), and constipation (0.0% vs 3.0%).</p> <p>The most common haematological AEs reported in the olaparib arm versus placebo were anaemia (43.6% vs 8.1%), neutropenia (19.5% vs 6.1%), and thrombocytopaenia (13.8% vs 3.0%). Grade ≥3 haematological AEs reported in the olaparib arm versus placebo were anaemia (19.5% vs 2.0%), neutropenia (5.1% vs 4.0%), and thrombocytopenia (1.0% vs 1.0%).</p>
<b>Expected reporting date</b>	-

## ESTIMATED COST and IMPACT

### COST

The cost of olaparib tablets is not yet known. Olaparib capsule formulation is already licensed and marketed, as previously noted. A pack of 448 x 50mg capsules has a list price of £3,550.<sup>23</sup>

### IMPACT – SPECULATIVE

#### IMPACT ON PATIENTS AND CARERS

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival                                   | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: <i>improved patient convenience (reduced number of pills taken daily)</i> | <input type="checkbox"/> No impact identified                      |

## IMPACT ON HEALTH and SOCIAL CARE SERVICES

- |   |   |
|---|---|
| <input type="checkbox"/> Increased use of existing services   | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services              |
| <input type="checkbox"/> Other                                | <input checked="" type="checkbox"/> None identified         |

## IMPACT ON COSTS and OTHER RESOURCE USE

- |  |   |
|--|---|
| <input type="checkbox"/> Increased drug treatment costs                      | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs                             | <input type="checkbox"/> Other reduction in costs     |
| <input checked="" type="checkbox"/> Other: uncertain cost of new formulation | <input type="checkbox"/> None identified              |

## OTHER ISSUES

- |   |   |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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