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HEALTH TECHNOLOGY BRIEFING
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Olaparib monotherapy for BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer

NIHRIO ID	26788	**NICE ID**	10257
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Olaparib is a medicinal product currently in development for the treatment of Breast Cancer Gene (BRCA)-mutated relapsed ovarian, fallopian tube or primary peritoneal cancer in patients who have received at least 2 prior platinum treatments and have progressed at least 6 months after their last platinum treatment. Ovarian cancer includes a group of tumours that arise from diverse types of tissue contained in the ovary and can often spread from the ovary to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity.

Olaparib is given by mouth (tablets) and belongs to a group of drugs called poly (ADP-ribose) polymerase (PARP) enzyme inhibitors which act by preventing DNA damage repair in cancer cells, promoting cell death. Using olaparib may improve outcomes and reduce side effects in patients with relapsed ovarian cancer who have received prior platinum therapy.

PROPOSED INDICATION

Treatment for BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer in patients who have received 2 or more lines of platinum-based chemotherapy.[1,2]

TECHNOLOGY

DESCRIPTION

Olaparib (Lynparza) is a potent inhibitor of human PARP enzymes (PARP-1, PARP-2, and PARP-3). PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. Olaparib has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies.[3]

Olaparib is currently in development for the treatment of patients with BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. In the phase III randomised trial (NCT02282020; SOLO-3), patients will receive either 300mg tablets of olaparib twice daily or physician's choice of single agent chemotherapy weekly until objective radiological disease progression, unacceptable toxicity or any other discontinuation criteria.[1]

INNOVATION AND/OR ADVANTAGES

Olaparib has shown significant clinical benefit in multiple tumour types, including ovarian, breast and pancreatic cancer.[4]

The Phase III SOLO-3 trial shows that olaparib significantly improves Objective Response Rate (ORR) and Progression Free Survival (PFS) versus physician's choice of chemotherapy in patients with BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer, who have previously received 2 or more lines of platinum-based chemotherapy.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Olaparib is currently licensed in the UK as a monotherapy for:[3]

- The maintenance treatment of adult patients with advanced BRCA 1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) following completion of first-line platinum-based chemotherapy.

- 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 chemotherapy.
- The treatment of adult patients with germline BRCA 1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments.

Very common (≥10%) adverse events associated with olaparib include: nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia and leukopenia.[3]

Olaparib is in phase II and phase III development as a monotherapy or combination treatment for several indications including:[6]

- Metastatic breast cancer
- Prostate cancer
- Ovarian cancer
- Pancreatic cancer
- Bladder cancer
- Gastric cancer
- Lung cancer
- Renal cell carcinoma
- Oesophagogastric cancer
- Endometrial cancer

PATIENT GROUP

DISEASE BACKGROUND

Ovarian cancer represents a group of tumours that arise from diverse types of tissue contained in the ovary and is classified from stage I to IV. The most common type of ovarian cancer arises from epithelial cells of the ovary, and can often spread from the ovary to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity. Most people are diagnosed with advanced stage disease. Advanced ovarian cancer falls within stages III and IV. Stage III denotes that the cancer is locally advanced and has spread outside the pelvis into the abdominal cavity. Stage IV denotes that distant metastasis to other body organs such as the liver and lungs has occurred. Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to ovarian cancer.[7] Symptoms of ovarian cancer include loss of appetite, abdominal pain and frequent urination.[8] The risk of developing ovarian cancer increases with age and it's most common in women aged between 75 and 79. Inherited gene mutations are another major risk factor and between 5 to 15% of ovarian cancer cases are caused by mutated BRCA 1 or 2 genes. Other risk factors include: a history of breast cancer, using hormone replacement therapy, smoking and being overweight or obese.[9]

Ovarian cancer may be categorised according to the response to initial platinum chemotherapy as follows: platinum-sensitive (disease responds to platinum-based therapy but relapses after 6 months or more), partially platinum-sensitive (disease responds to platinum-based therapy but relapses between 6 and 12 months), platinum-resistant (disease which relapses within 6 months of completion of platinum-based chemotherapy) and platinum-refractory (disease does not respond to initial platinum-based chemotherapy).[7]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017 there were 6,236 registrations of newly-diagnosed malignant neoplasm of the ovary and other unspecified female genital organs (ICD-10 code: C56-C57), equating to a directly age-standardised rate of 22.7 cases per 100,000 females.[10] Statistics from Cancer Research UK report that in 2016, ovarian cancer was the 6th most common cancer in the UK and accounted for 4% of all new cancer cases. Incidence rates for ovarian cancer in the UK are highest in females aged between 75 to 79 years (2014 to 2016). Almost 6 in 10 ovarian cancer cases are diagnosed in late stage in England (2014). Incidence rates for ovarian cancer are projected to rise by 15% in the UK between 2014 and 2035, to 32 cases per 100,000 females.[11]

In England in 2017-2018 there were 43,189 finished consultant episodes, and 40,280 hospital admissions with a primary diagnosis of malignant neoplasm of female genital organs (ICD-10 code C56-C57), resulting in 31,117 day cases and 58,079 bed days.[12]

In the UK in 2017, there were 4,097 deaths from ovarian cancer. Mortality rates for ovarian cancer in the UK are highest in females aged 85 to 89 years (2015 to 2017). Mortality rates are projected to fall by 37% in the UK between 2014 and 2035, to 10 deaths per 100,000 females by 2035.[11]

Almost three-quarters (71.7%) of women diagnosed with ovarian cancer in England survive their disease for one year or more (2013-2017) and 42.6% survive their disease for 5 years or more (2013-2017).[13] Ovarian cancer survival in England is the highest for women diagnosed under 40 years. When diagnosed at its earliest stage, 9 in 10 women with ovarian cancer will survive their disease for five years or more, compared with less than 5 in 100 women when diagnosed at the latest stage.[11]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The current NICE treatment pathway for managing relapsed/recurrent advanced ovarian cancer (stage II to IV) includes second-line treatment with chemotherapy. PARP inhibitors are recommended when patients have responded to platinum-based chemotherapy.[14]

CURRENT TREATMENT OPTIONS

Olaparib is recommended within its marketing authorisation 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:[15]

- They have had 3 or more courses of platinum-based chemotherapy.
- The drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.

Niraparib is recommended for use within the Cancer Drugs Fund as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if:[14]

- They have a germline BRCA-mutation and have had 2 courses of platinum-based chemotherapy or

- They do not have a germline BRCA-mutation and have had 2 or more courses of platinum-based chemotherapy and
- The conditions in the managed access agreement for niraparib are followed.

PLACE OF TECHNOLOGY

If licensed, olaparib will offer an additional treatment option for patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer (including primary peritoneal and/or fallopian tube cancer) who have received 2 or more lines of platinum-based chemotherapy.

CLINICAL TRIAL INFORMATION

Trial	**SOLO3; NCT02282020; 2014-003438-20; olaparib vs single agent chemotherapy; Phase III.**
Sponsor	AstraZeneca UK Ltd.
Status	Ongoing.
Source of Information	Abstract;[2,5] Trial registry;[1,16] Manufacturer[17]
Location	EU (not including UK), USA, Canada and other countries.
Design	Randomised, open-label, controlled, parallel assignment.
Participants	N=266; aged ≥ 18 to 130 yrs; female; histologically diagnosed relapsed high grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer; documented germline mutation in breast cancer susceptibility genes: BRCA1 and/or BRCA2 that is predicted to be deleterious or suspected deleterious; received at least 2 prior platinum based lines of chemotherapy - patients must be partially platinum sensitive or platinum sensitive.
Schedule	Randomised in a 2:1 ratio to: • Olaparib 300mg tablets taken orally twice a day. • Single agent chemotherapy (physician's choice of either paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine) administered weekly. All patients will receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the investigator or the patient experiences unacceptable toxicity or they meet any other discontinuation criteria.
Follow-up	Not reported.

Primary Outcomes	Objective Response Rate (ORR) [Time frame: Primary endpoint will be assessed at the time of the primary analysis: a minimum of 6 mths after LSI, whichever is sooner].
Secondary Outcomes	• Overall Survival (OS)* • Time from randomisation to second progression (PFS 2)* • Time to earliest progression by RECIST 1.1 or Cancer Antigen (CA-125) or death* • Time to deterioration of Health-Related Quality of Life (HRQoL)** • Time to first subsequent therapy or death (TFST)* • Time to second subsequent therapy or death (TSST)* • Time from randomisation to study treatment discontinuation or death (TDT)* • Safety and tolerability of olaparib by assessment of the number of Adverse Events (AEs)*** • Safety and tolerability of olaparib by review of laboratory parameters, ECG and vital signs*** • Efficacy in patients following platinum based chemotherapy by assessment of time to earliest progression by RECIST or death**** *[Time frame: a minimum of 6 mths after LSI, whichever is sooner and at study completion – estimated date 01 Jan 2021]. **[Time Frame: Questionnaire completed at baseline, Day 29 and then every 8 weeks for 48 weeks.] ***[Time Frame: Patients will be assessed until study treatment discontinuation, up until the end of the study - estimated 01 Jan 2021]. ****[Time Frame: Radiological assessments will be scheduled every 8 weeks (+/- 1 week) from randomisation for 48 weeks and every 12 weeks (+/- 1 week) thereafter until objective disease progression until study completion- estimated 01 Jan 2021]

Key Results	ORR was 72% with olaparib vs 51% with treatment of physician's choice (TPC) (odds ratio 2.53, 95% confidence interval (CI) 1.40–4.58; p=0.002). Hazard ratio for PFS by blinded independent central review was 0.62 (95% CI 0.43–0.91; p=0.013). The median PFS was 13.4 vs 9.2 mths (olaparib vs TPC) and by investigator assessment was 0.49 (95% CI 0.35–0.70; p<0.001 and median 13.2 vs 8.5 mths respectively). Subjects with BRCA-mutated platinum-sensitive ovarian cancer receiving olaparib monotherapy had a significant, clinically relevant improvement in ORR and PFS vs TPC.
Adverse effects (AEs)	Most common AEs with olaparib were nausea (65% vs 34% [TPC]) and anaemia (50% vs 25%) and with TPC were palmar-plantar erythrodysesthesia (PPE; 36% vs 1% [olaparib]) and nausea. Most common grade ≥3 AEs in either arm were anaemia (21% [olaparib] vs 0 [TPC]), PPE (0 vs 12%) and neutropenia (6% vs 11%). For olaparib vs TPC, serious AEs were reported by 24% vs 18% and AEs led to treatment discontinuation in 7% vs 20%.
Expected reporting date	-

ESTIMATED COST

Olaparib is already marketed in the UK. The NHS indicative price for olaparib is:[18]
Tablets:

- A pack of 56 x 100mg tablets costs £2,317.50
- A pack of 56 x 150mg tablets costs £2,317.50

Capsules:

- A pack of 448 x 50mg capsules costs £3,550.00

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to secondline or subsequent platinum-based chemotherapy (TA381). January 2016.
- NICE technology appraisal. Niraparib for maintenance treatment of relapsed, platinum sensitive ovarian, fallopian tube and peritoneal cancer (TA528). July 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers. E10/S/f.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

Comprehensive Cancer Network (NCCN)]. [Ovarian Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology]. [2016].[19]

ADDITIONAL INFORMATION

Astra Zeneca UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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