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HEALTH TECHNOLOGY BRIEFING
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Olaparib for BRCA mutated and high risk HER2 negative breast cancer - adjuvant therapy

NIHRIO ID	14892	**NICE ID**	9661
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	645826

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Olaparib is in clinical development for the adjuvant treatment of adults who are breast cancer type 1 and type 2 susceptibility protein (BRCA) mutant and human epidermal growth factor receptor 2 (HER2)-negative and have completed local treatment and (neo)-adjuvant chemotherapy. BRCA1 and BRCA2 are proteins that help repair damaged DNA. Adjuvant therapy is additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Cancer cells that are HER2 negative may grow more slowly and are less likely to spread to other parts of the body than cancer cells that have a large amount of HER2 on their surface.

Olaparib is taken orally and works by blocking a protein called poly [adenosine diphosphateribose] polymerase (PARP). PARP is important to repair damaged DNA. By blocking PARP, the tumour cells may die. If licenced, olaparib will offer a new adjuvant therapy for patients with early BRCA mutated and high-risk HER2-negative breast cancer who have completed local treatment and (neo)-adjuvant chemotherapy.

PROPOSED INDICATION

Adjuvant therapy for patients with early BRCA 1/2 mutated and high risk HER2-negative breast cancer who have completed local treatment and (neo)-adjuvant chemotherapy.[1,a]

TECHNOLOGY

DESCRIPTION

Olaparib (Lynparza) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and 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.[2]

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.[2]

Olaparib is currently in phase III clinical development for adjuvant therapy for patients with BRCA mutated and high-risk HER2-negative breast cancer who have completed local treatment and (neo)-adjuvant chemotherapy. In phase III clinical trial (OlympiA; NCT02032823), participants will receive olaparib 300 mg (2 x 150mg) orally twice daily for up to a maximum of 12 months. All randomised patients will have clinical assessment visits for 10 years following their randomisation into the study.[1, a]

INNOVATION AND/OR ADVANTAGES

Research has shown that medicines that interfere or inhibit the PARP enzyme make it even harder for cancer cells with a BRCA1 or BRCA2 mutation to fix DNA damage. This makes it harder for the cancer cells to survive. In other words, a PARP inhibitor makes some cancer cells less likely to survive their DNA damage.[3] This may be one of the reasons why PARP inhibitors appear to be most effective in tumours with defects in homologous recombination repair, including breast cancer with deleterious mutations in BRCA1 and BRCA2, as homologous recombination repair predominates over non-homologous end-joining during S-phase as a relatively error-proof mechanism of repairing DNADSBs.[4]

Olaparib is an oral PARP inhibitor that has been shown to significantly improve median progression-free survival among patients with metastatic HER2-negative breast cancer and a BRCA mutation.[5] In addition, olaparib is the first PARP inhibitor approved by the FDA for use

[a] Information provided by AstraZeneca UK Ltd on UK PharmaScan

in BRCA mutated, HER2-negative metastatic breast cancer who received prior chemotherapy.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Olaparib is licensed as monotherapy in the EU/UK for the treatment of:[2]

Ovarian cancer

- Maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- 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.

Breast cancer

- Adult patients with germline BRCA1/2-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.

- Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

Adenocarcinoma of the pancreas

- Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

The most commonly reported adverse events (≥ 10%) among patients receiving olaparib monotherapy were: nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anaemia.[2]

Olaparib is currently in phase II/III clinical development for the treatment of various types of cancers including breast cancer, renal cell cancer, and advanced solid tumours.[7]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is a malignancy of the breast tissue and is the most common malignancy diagnosed in women worldwide.[8] The exact aetiology of breast cancer is unknown, however family history is one of the strongest determinants of risk.[9] Risk factors for breast cancer include genetic causes, increased age, reproductive history and hormone exposure, lifestyle factors (e.g. alcohol), medical history, and radiation exposure.[10] The first symptom of breast cancer most women notice is a lump or an area of thickened tissue in their breast. Other signs and symptoms of breast cancer include axillary mass, nipple discharge, skin changes on breast or nipple, asymmetric thickening or nodularity, breast pain.[11,12]

In general, breast cancer can be broken down into three biologic subgroups, each of which has a direct bearing on treatment choices:[13]

- those that express the oestrogen receptor (ER),
- those that express the human epidermal growth factor receptor 2 (HER2 [with or without ER expression]),
- those that do not express either of these, nor the progesterone receptor (triple-negative).

In normal cells, HER2 helps to control cell growth. In patients with HER2-negative, cancer cells may grow more slowly and are less likely to reoccur (come back) or spread to other parts of the body than cancer cells that have a large amount of HER2 on their surface.[14]

BRCA1 and BRCA2 are human genes that produce tumour suppressor proteins. These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of each cell's genetic material. When either of these genes is mutated, or altered, such that its protein product is not made or does not function correctly, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. A harmful BRCA1 or BRCA2 mutation can be inherited from a person's mother or father. Women with certain genetic mutations have a higher lifetime risk of the disease.[15]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that about 72% of women who inherit a harmful BRCA1 mutation and about 69% of women who inherit a harmful BRCA2 mutation will develop breast cancer by the age of 80.[15]

In England, in 2017 there were 45,790 registrations of newly diagnosed cases of malignant neoplasm of breast in females (ICD-10 code C50), and the directly age-standardised rate per 100,000 population was 166.7 only among females.[16] Incidence rates are projected to rise by 2% in the UK between 2014 and 2035, from 205 per 100,000 (54,833 cases) to 210 per 100,000 (71,022 cases).[17] Approximately 20–40% of patients with early-stage triple negative breast cancer develop metastatic disease.[18]

In England and Wales in 2017, there were 10,219 deaths with malignant neoplasm of breast (ICD-10 code C50) recorded as the underlying cause,[19] and the directly age-standardised death rate per 100,000 population was 33.3 among of females.[16] The latest published survival statistics for breast cancer for women in England (patients diagnosed in 2013-2017 and followed up to 2018) report 1-year survival rate of 95.8% and 5-year survival rate of 85.0% (age-standardised).[20]

In 2018-19 there were 219,885 finished consultant episodes (FCEs) and 215,644 hospital admissions leading to 80,435 FCE bed days and 183,828 day cases with a primary diagnosis of ICD-10 code C50 (malignant neoplasm of the breast).[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The management of breast cancer has different approaches depending on the type and stage at diagnosis, and involves the use of different therapies:[22]

- Patients should be assigned to a multidisciplinary team to provide the best treatment and care. The main treatments for breast cancer include surgery, radiotherapy,

chemotherapy, hormone therapy, and biological therapy (targeted therapy). Patients may have one of these treatments or a combination. The type or combination of treatments will depend on how the cancer was diagnosed and the stage it is at.

- Surgery is usually the first type of treatment for breast cancer. The type of surgery undergo will depend on the type of breast cancer developed. Surgery is usually followed by chemotherapy or radiotherapy or, in some cases, hormone or biological treatments.

- Radiotherapy is usually given after surgery and chemotherapy to kill any remaining cancer cells.

Chemotherapy is usually used after surgery to destroy any cancer cells that haven't been removed (adjuvant). In some cases, the chemotherapy is provided before surgery, which is often used to shrink a large tumour (neo-adjuvent). The choice of medication and the combination will depend on the type of breast cancer developed and how much it has spread.[22]

CURRENT TREATMENT OPTIONS

For patients with early stage breast cancer the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines recommends:[23]

Chemotherapy
It is recommended in the vast majority of triple-negative, HER2-positive breast cancers and in high-risk luminal-like HER2-negative tumours. The most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients cyclophosphamide/methotrexate/5 fluorouracil (CMF) may still be used. Four cycles of doxorubicin and cyclophosphamide (AC) are considered to have equal efficacy to six cycles of CMF.

PLACE OF TECHNOLOGY

If licensed, olaparib will offer an additional adjuvant therapy option for patients with early BRCA 1/2 mutated and high-risk HER2-negative breast cancer who have completed local treatment and (neo)-adjuvant chemotherapy.[b]

CLINICAL TRIAL INFORMATION

Trial	**OlympiA;** NCT02032823; A Randomised, Double-blind, Parallel Group, Placebo-controlled Multi-centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients With gBRCA1/2 Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy **Phase III**- ongoing **Location(s):** US, Canada, EU (incl. UK) plus more than four other countries **Primary completion date:** November 2020

[b] Information provided by AstraZeneca UK Ltd on UK PharmaScan

Trial design	Randomised, parallel assignment, triple-blinded, placebo-controlled
Population	N = 1386; adults aged 18 to 130 years; histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that is either triple negative breast cancer defined as ER and PgR negative and HER2 negative (not eligible for anti-HER2 therapy) or ER and/or PgR positive, HER2 negative; Documented germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious.
Intervention(s)	2 x 150mg olaparib tablets, orally, twice daily approx. 12 hours apart
Comparator(s)	Matched placebo
Outcome(s)	Invasive Disease-Free Survival (IDFS) [Time frame: Up to 10 years]. - See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Olaparib is already marketed in the UK. The NHS indicative price for olaparib is:[24]

- 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 in development. Pembrolizumab in combination with chemotherapy for neoadjuvant treatment of triple negative breast cancer. (GID-TA10399). Expected publication date TBC.
- NICE technology appraisal in development. Atezolizumab with nab-paclitaxel for neoadjuvant treatment of early triple negative breast cancer. (GID-TA10531). Expected December 2021.
- NICE guideline. Early and locally advanced breast cancer: diagnosis and management. Published July 2018.
- NICE quality standards. Breast cancer (QS12). Updated June 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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

- European Society for Medical Oncology. Early Breast Cancer: ESMO Clinical Practice Guidelines. 2019.[23]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. 2018.[25]
- Scottish Intercollegiate Guidelines Network (SIGN). Treatment of primary breast cancer. 2013.[26]

ADDITIONAL INFORMATION

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