

**HEALTH TECHNOLOGY BRIEFING
MAY 2019**

Olaparib in combination with bevacizumab for ovarian, fallopian tube or primary peritoneal cancer – maintenance therapy

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| NIHRIO ID | 26897 | NICE ID | 10161 |
| Developer/Company | AstraZeneca UK Ltd | UKPS ID | Not available |

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| Licensing and market availability plans | Currently in Phase III trials |
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SUMMARY

Olaparib in combination with bevacizumab is in clinical development as a maintenance therapy for adult patients with advanced ovarian, fallopian tube or peritoneal cancer that have responded to initial treatment with other types of chemotherapy. Advanced 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. People with advanced ovarian cancer that have responded to initial treatment often require maintenance therapy to prevent or delay the recurrence and spread of the cancer.

Olaparib belongs to a group of drugs called PARP enzyme inhibitors while bevacizumab is an anti-VEGF monoclonal antibody. Both drugs act in different but synergistic ways to kill tumour cells. It is thought that bevacizumab may increase the sensitivity of olaparib to killing the tumour cells. Olaparib administered orally as a monotherapy is already licensed as a maintenance therapy of advanced ovarian cancer. The addition of bevacizumab given by intravenous infusions may potentially improve treatment outcomes.

This briefing reflects the evidence available at the time of writing 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. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

PROPOSED INDICATION

Advanced FIGO stage IIIB-IV high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer treated with standard first-line treatment, combining platinum-taxane chemotherapy and bevacizumab concurrent with chemotherapy and in maintenance.¹

TECHNOLOGY

DESCRIPTION

Olaparib (Lynparza) is a poly-ADP polymerase (PARP) enzyme inhibitor, which selectively kills tumour cells with an impaired homologous recombination DNA repair pathway whilst sparing normal cells.² 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

Bevacizumab (Avastin) binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.⁴

Olaparib in combination with bevacizumab is currently in phase III development for the maintenance treatment of adult patients with advanced FIGO stage IIIB-IV high grade serious or endometrioid ovarian, fallopian tube or peritoneal cancer, following first-line treatment with bevacizumab and platinum-taxane-based chemotherapy. In the phase III clinical trial (NCT02477644), olaparib tablets, 300mg, are administered twice daily to patients for up to 24 months.^{1,5,6} All patients will receive standard maintenance care of bevacizumab (15 mg/kg every three weeks) for up to 15 months.⁶

INNOVATION AND/OR ADVANTAGES

Studies show that olaparib increases the time patients can live without their disease getting worse after initial treatment with platinum chemotherapy has reduced or cleared the tumours.⁷ Olaparib as monotherapy is currently indicated in the EU for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated high grade serous ovarian cancer. When combined with bevacizumab, it is hypothesized that bevacizumab may increase the ovarian tumour sensitivity to olaparib, potentially improving progression free survival.⁶

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Olaparib is licensed in the EU as a 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 complete or partial response to platinum-based chemotherapy⁷.
- the treatment of 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.⁷

Bevacizumab in combination with other anticancer therapies is currently licenced in the EU for various types and stages of cancers. Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynaecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.⁴

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. 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. Most people are diagnosed with advanced stage disease. Some people have gene mutations that may increase the risk of ovarian cancer. Mutated inherited genes that increase the risk of ovarian cancer include BRCA 1 or 2.⁸

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).⁸

CLINICAL NEED AND BURDEN OF DISEASE

There are around 7,400 new ovarian cancer cases in the UK every year (2013 to 2015). In 2015, 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 75 to 79 years (2013 to 2015). Almost 6 in 10 ovarian cancer cases are diagnosed in late stage in England (2014) and Northern Ireland (2010 to 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 by 2035.⁹

There are 4,100 ovarian cancer deaths in the UK annually (2014 to 2016). In females in the UK, ovarian cancer is the 6th most common cause of cancer death, with around 4,200 deaths in 2016. Mortality rates for ovarian cancer in the UK are highest in females aged 85 to 89 years (2014 to 2016). Mortality rates are projected to fall by 37% in the UK between 2014 and 2035, to 10 deaths per 100,000 females by 2035.

More than a third (35%) of women diagnosed with ovarian cancer in England and Wales survive their disease for 10 years or more (2010 to 2011), 46% survive their disease for five years or more (2010 to 2011) and 73% survive for one year more (2010 to 2011). Ovarian cancer survival in England is the highest for women diagnosed under 40 years in the UK. 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.⁹

1 in 50 females in the UK will be diagnosed with ovarian cancer. 11% of ovarian cancer cases in the UK are preventable.⁹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The current NICE treatment pathway for managing advanced stage II to IV ovarian cancer includes primary surgery followed by first-line then second-line chemotherapy. Maintenance therapy is

recommended when patients have responded to the most recent course of platinum-based chemotherapy.¹⁰

CURRENT TREATMENT OPTIONS

Olaparib³, niraparib¹¹ and rucaparib¹² are all indicated as monotherapies for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

NICE recommends olaparib² 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:

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

NICE recommends niraparib¹³ 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:

- 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 in combination with bevacizumab will offer an additional maintenance treatment option for patients with advanced FIGO stage IIIB-IV high grade serious ovarian, fallopian tube, or peritoneal cancer.

CLINICAL TRIAL INFORMATION

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| Trial | PAOLA-1; NCT02477644, EudraCT2014-004027-52, ; GINECO-OV125b; olaparib vs placebo; phase III |
| Sponsor | Arcagy-Gineco Group |
| Status | Ongoing |
| Source of Information | Trial registry ^{1,14} Associated publication ⁶ |
| Location | EU (not incl. UK) and Japan. |
| Design | Randomised, double-blind, placebo-controlled, parallel assignment |
| Participants | N=612 (planned); aged ≥ 18 years; newly diagnosed ovarian cancer, primary peritoneal cancer and/or fallopian-tube cancer; histologically confirmed (based on local histopathological findings): high grade serious or high grade endometrioid or other epithelial non mucinous ovarian cancer in a patient with germline BRCA 1 or 2 deleterious mutation; at an advanced stage: FIGO stage IIIB, IIIC or IV of the 1998 FIGO classification; completed first-line platinum taxane chemotherapy plus a minimum of 3 cycles of bevacizumab; without evidence of disease or in complete response or partial response from first-line |

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| | treatment; normal organ and bone marrow function; ECOG performance status 0-1. |
| Schedule | Randomised in a 2:1 ratio to: <ul style="list-style-type: none"> • Olaparib tablets per os 300mg twice daily for up to 24 months • Placebo tablets per os 300mg twice daily for up to 24 months All pts will receive standard maintenance care of bevacizumab (15 mg/kg every three weeks) for up to 15 months |
| Follow-up | Not reported. |
| Primary Outcomes | Progression free survival (PFS1) [Time frame: phase up to a total of 15 months] |
| Secondary Outcomes | Time frame: study end <ul style="list-style-type: none"> • Overall survival • Time to earliest progression by RECIST or CA-125 • Second progression free survival (PFS2) • Time to start of first subsequent therapy or death (TSFT) • Time to start of second subsequent therapy or death (TFST) • Safety and tolerability Patient reported outcome [Time frame: 2 years after last patient included] |
| Key Results | - |
| Adverse effects (AEs) | - |
| Expected reporting date | Primary completion date reported as June 2022. |

ESTIMATED COST

Olaparib is already marketed in the UK. The NHS indicative price for olaparib is:¹⁵

- Tablets:
 - A pack of 56 x 100mg tablets costs £2317.50
 - A pack of 56 x 150mg tablets costs £2317.50
- Capsules
 - A pack of 448 x 50mg capsules costs £3550.00

The NHS indicative price for bevacizumab is:¹⁶

- Solution for infusion:
 - 1 vial of 100mg/4ml solution for infusion costs £242.66 (hospital only)
 - 1 vial of 400mg/16ml solution for infusion costs £924.40 (hospital only)

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 second-line 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.

- NICE technology appraisal (in development). Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (ID1485). Expected publication date: October 2019.

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.

ADDITIONAL INFORMATION

AstraZeneca 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

REFERENCES

- 1 ClinicalTrials.gov. *Randomized, Double-Blind, Phase III Trial Olaparib vs. Placebo Patients With Advanced FIGO Stage IIIB-IV High Grade Serious or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer Treated Standard First-Line Treatment*. Trial ID: NCT02477644. 2015. Status: Ongoing. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT02477644> [Accessed 8 April 2019].
- 2 NICE. *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)*. Last Update Date: Available from: <https://www.nice.org.uk/guidance/ta381/> [Accessed 8 April 2019].
- 3 (eMC) eMC. *Lynparza 100mg Film-Coated Tablets*. Available from: <https://www.medicines.org.uk/emc/product/9204/smpc> [Accessed 08 April 2019].
- 4 (eMC) eMC. *Avastin 25mg/ml concentrate for solution for infusion*. Available from: <https://www.medicines.org.uk/emc/product/3885> [Accessed 20 May 2019].
- 5 (GEICO) SOCRG. *PROTOCOL CLINICAL TRIAL: GINECO-ov125b/GEICO-1503*. Available from: <https://www.geicogroup.com/en/investigacion-clinica-en/estudios-abiertos-en/cancer-de-ovario-en/gineco-ov125bgeico-1503-en/> [Accessed 08 April 2019].
- 6 Ray-Coquard IL, Harter P, Gonzalez Martin A, Cropet C, Pignata S, Fujiwara K, et al. PAOLA-1: An ENGOT/GCIG phase III trial of olaparib versus placebo combined with bevacizumab as maintenance treatment in patients with advanced ovarian cancer following first-line platinum-based chemotherapy plus bevacizumab. American Society of Clinical Oncology 2017.
- 7 (EMA) EMA. *Lynparza (olaparib) Summary of opinion (post authorisation)*. 2019. Available from: <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lynparza> [Accessed 08 April 2019].
- 8 NICE. *Olaparib for maintenance treatment of BRCA 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy - Final Scope*. NICE; 2014. Available from: <https://www.nice.org.uk/guidance/TA381/documents/ovarian-fallopian-tube-and-peritoneal-cancer-brca-1-or-2-mutated-relapsed-platinumsensitive-olaparib-maintenance-id735-final-scope2>.

- 9 UK CR. *Ovarian cancer statistics*. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-Five> [Accessed 08 April 2019].
- 10 NICE. *Managing advanced (stage II-IV) ovarian cancer*. Available from: <https://pathways.nice.org.uk/pathways/ovarian-cancer#path=view%3A/pathways/ovarian-cancer/managing-advanced-stage-ii-iv-ovarian-cancer.xml&content=view-node%3Anodes-second-line-and-subsequent-chemotherapy> [Accessed 15 April 2019].
- 11 (eMC) eMC. *Zejula 100 mg hard capsules*. Available from: <https://www.medicines.org.uk/emc/product/8828> [Accessed 20 May 2019].
- 12 (eMC) eMC. *Rubraca 200mg film-coated tablets*. Available from: <https://www.medicines.org.uk/emc/product/10026/smpc> [Accessed 20 May 2019].
- 13 NICE. *Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA528)*. Last Update Date: Available from: <https://www.nice.org.uk/guidance/ta528> [Accessed
- 14 EudraCT. *Randomized, Double-Blind, Phase III Trial Olaparib vs. Placebo Patients With Advanced FIGO Stage IIIB-IV High Grade Serious or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer Treated Standard First-Line Treatment*. Trial ID: 2014-004027-52. 2014. Status: Ongoing. Available from: <https://www.clinicaltrialsregister.eu/ctr-search/search?query=GINECO-OV125b+> [Accessed 2 May 2019].
- 15 NICE. *BNF British National Formulary - NICE (Olaparib)*. Available from: <https://bnf.nice.org.uk/medicinal-forms/olaparib.html> [Accessed 2 May 2019].
- 16 NICE. *BNF British National Formulary - NICE (Bevacizumab)*. Available from: <https://bnf.nice.org.uk/medicinal-forms/bevacizumab.html> [Accessed 20 May 2019].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.