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Newcastle University

Health Technology Briefing
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Alpelisib and Olaparib for treating platinum-resistant or refractory BRCA wild-type ovarian cancer

Company/Developer	Novartis Pharmaceuticals UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31129	NICE TSID: 11830	UKPS ID: 661282

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Alpelisib in combination with olaparib is in clinical development for the treatment of adults with platinum-resistant or refractory, high-grade serous/endometrioid ovarian cancer, including fallopian tube cancer or primary peritoneal cancer. These cancers occur in the female reproductive system and are often grouped together as they are treated in the same way. Tumours can occur in the ovaries, fallopian tubes or peritoneum. Serous ovarian cancer is the most common subtype. Platinum-refractory refers to progression of disease while receiving the latest line of platinum-based chemotherapy or within 4 weeks of last dose. Platinum-resistant refers to progression within one to six months after completing platinum-based therapy.

Alpelisib is a drug given as an oral film coated tablet. Alpelisib targets a specific enzyme that transmits signals to cells, stopping the growth and survival of cancer cells. Olaparib is a drug given as an oral film coated tablet. Olaparib blocks the ability of human proteins to repair damaged DNA and therefore can limit the growth of tumours. Olaparib is currently recommended as a maintenance treatment for ovarian, fallopian tube and peritoneal cancer. If licensed, this combination therapy will provide a novel treatment option with high safety and efficacy for patients with platinum resistant or refractory ovarian cancer.

Proposed Indication

Treatment of adult women with germline breast cancer type 1 susceptibility protein (BRCA) non-mutated, platinum refractory/resistant, high grade serous/endometrioid ovarian, fallopian tube, or primary peritoneal cancer who have had at least one, but no more than three prior lines of systemic therapy.[1]

Technology

Description

Alpelisib (BYL719, Piqray) is an orally bioavailable phosphatidylinositol 3-kinase (PI3K) inhibitor with potential antineoplastic activity. Alpelisib specifically inhibits PI3K in the PI3K/AKT kinase (or protein kinase B) signalling pathway, thereby inhibiting the activation of the PI3K signalling pathway. This may result in inhibition of tumour cell growth and survival in susceptible tumour cell populations. Activation of the PI3K signalling pathway is frequently associated with tumorigenesis. Dysregulated PI3K signalling may contribute to tumour resistance to a variety of antineoplastic agents.[1,2]

Olaparib (Lynparza) is a potent inhibitor of human poly (ADP-ribose) polymerase 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. Olaparib has been shown to inhibit the growth of selected tumour cell lines.[3]

Alpelisib in combination with olaparib is currently in a phase III clinical trial (NCT04729387) for the treatment of adults with germline BRCA non-mutated, platinum refractory/resistant high grade serous/endometrioid ovarian, fallopian tube, or primary peritoneal cancer who have had at least one, but no more than three prior lines of systemic therapy and for whom single agent chemotherapy is the most appropriate next line of treatment. In the clinical trial, alpelisib was administered at 200 mg orally once daily, whilst olaparib was administered at 200 mg orally twice daily following food on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.[1]

Key Innovation

PI3K–AKT–mTOR is the most frequently activated pathway in cancer. A number of P13K inhibitors are being developed by pharmaceutical companies, including pan-P13K inhibitors. Alpelisib is a P13K alpha-selective inhibitor; targeting a single P13K isoform may allow administration at therapeutic doses without being limited by toxicities associated with inhibiting multiple isoforms.[4]

Homologous recombination repair (HRR) proficiency is associated with limited response to PARP inhibitors (such as Olaparib). PI3K inhibitors such as alpelisib downregulate BRCA expression, which abrogates HRR proficiency and may lead to re-sensitisation to PARP inhibitor treatment.[5] Olaparib is currently licensed as a maintenance treatment for ovarian cancer patients who have advanced germline and/or somatic BRCA mutations.[3] If licensed, alpelisib in combination with olaparib will offer an additional treatment option adult women with platinum resistant or refractory high-grade serous ovarian cancer.

Regulatory & Development Status

Alpelisib in combination with olaparib does not currently have a Marketing Authorisation in the UK.

Alpelisib currently has Marketing Authorisation in the UK and is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-based therapy.[6]

Olaparib currently has Marketing Authorisation in the UK for the following:[3]

- As a monotherapy for the 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
- 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 response (complete or partial) to platinum-based chemotherapy
- In combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) 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 in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability
- As a monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy
- As a monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer and have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or for patients with hormone receptor (HR)-positive breast cancer have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy.
- As a 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
- As a monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent

Patient Group

Disease Area and Clinical Need

Ovarian cancer is when abnormal cells in the ovary begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). If not caught early, cancer cells gradually grow into the surrounding tissues and spread to other areas of the body.[7] Anyone with ovaries can get ovarian cancer, but it mostly affects those over 50. Sometimes ovarian cancer runs in families. Ovarian cancer is often diagnosed late, but early diagnosis can mean it is more treatable. Symptoms of ovarian cancer include having a swollen tummy or feeling bloated, pain or tenderness in the tummy or the area between the hips (pelvis), no appetite or feeling full quickly after eating, an urgent need to pee or needing to pee more often.[8] Serous ovarian cancer is the most common subtype, accounting for ~70% of all ovarian cancers. Serous ovarian cancer is not a single disease but is comprised of high-grade serous ovarian cancer and low-grade serous ovarian cancer. Patients treated with platinum chemotherapy are categorised as either platinum sensitive or platinum resistant based on the amount of time from end of treatment to relapse, referred to as the

platinum-free interval. Platinum response is generally classified into refractory, resistant, partially-sensitive or sensitive. Platinum-refractory refers to progression while receiving last line of platinum-based therapy or within 4 weeks of last platinum dose and platinum-resistant refers to progression within one to six months after completing platinum-based therapy.[9]

In 2016-2018, there were around 7,500 new ovarian cancer cases in the UK every year. In females in the UK, ovarian cancer is the 6th most common cancer. Ovarian cancer accounts for 4% of all new cancer cases in females in the UK. 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.[10] In England (2021-22), there were 36,418 finished consultant episodes (FCEs) and 33,860 admissions for malignant neoplasm of ovary (ICD-10 code C56), which resulted in 27,232 day cases and 45,542 FCE bed days.[11]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following treatment options for adults with germline BRCA non-mutated, platinum resistant/refractory, advanced ovarian cancer, primary peritoneal cancer and fallopian tube cancer:[12]

- Paclitaxel in combination with platinum or as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.
- Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.
- PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.
- Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer when there has been a complete or partial response after first-line platinum-based chemotherapy plus bevacizumab, and the cancer is associated with homologous recombination deficiency (HRD).
- Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy
- Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy
- Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer
- Olaparib for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose disease has responded to platinum-based chemotherapy
- Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy

Clinical Trial Information

Trial	NCT04729387; 2019-004682-40; EPIK-O: A Phase III, Multi-center, Randomized (1:1), Open-label, Active-controlled, Study to Assess the Efficacy and Safety of Alpelisib (BYL719) in Combination With Olaparib as Compared to Single Agent Cytotoxic Chemotherapy, in Participants With no Germline BRCA Mutation Detected, Platinum-resistant or Refractory, High-grade Serous Ovarian Cancer

	Phase III - Recruiting **Locations** – 12 EU countries, UK, US, Canada and other countries **Primary completion date** – June 2023
Trial Design	Randomised, parallel assignment, open label
Population	N=358 (estimated); 18 years and older; histologically confirmed diagnosis of high-grade serous or high-grade endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer; no germline BRCA1/2 mutation; platinum-resistant or platinum refractory disease; received at least one but no more than three prior systemic treatment regimens
Intervention(s)	Alpelisib will be administered at 200 mg orally once daily following food on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle. Olaparib will be administered at 200 mg orally twice daily irrespective of meals on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.
Comparator(s)	Investigator's choice of one of 2 single agent cytotoxic chemotherapies: Paclitaxel 80 mg/m2 intravenously weekly or Pegylated liposomal Doxorubicin (PLD) 40-50 mg/m2 (physician discretion) intravenously every 28 days.
Outcome(s)	Primary outcome(s): 1. Progression Free Survival (PFS) based on Blinded Independent Review Committee (BIRC) assessment using RECIST 1.1 criteria [Time Frame: From randomization until the date of the first documented progression or death due to any cause, whichever comes first, assessed up to approximately 23 months] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Alpelisib is already marketed in the UK for HR-positive, HER2-negative, breast cancer with a PIK3CA mutation. The cost of alpelisib 56 tablets x 150mg and 28 tablets x 200mg is £4,082.14.[13]

Olaparib is already marketed in the UK for various cancer indications. The cost of olaparib 56 tablets x 100mg and 56 x 150mg tablets costs £2317.50.[14]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA784). April 2022.
- NICE technology appraisal. Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer (TA693). April 2021.

- NICE technology appraisal. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (TA673). February 2021.
- NICE technology appraisal. Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA620). January 2020.
- NICE technology appraisal. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA611). November 2019.
- NICE technology appraisal. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA598). August 2019.
- NICE technology appraisal. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). April 2016.
- NICE clinical guideline. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE quality standard. Ovarian cancer (QS18). May 2012.

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

Other Guidance

- Scottish Intercollegiate Guidelines Network. SIGN 135 – Management of epithelial ovarian cancer. November 2013.
- Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. February 2021.
- ESMO-ESGO Ovarian Cancer Consensus Conference Working Group: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. May 2019.

Additional Information

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