Health Technology Briefing
December 2021

Cediranib with olaparib for previously treated platinum resistant recurrent ovarian cancer

Company/Developer	AstraZeneca

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28237	NICE ID: 10526	UKPS ID: 653571

Licensing and Market Availability Plans

Currently in phase II/III clinical trials

Summary

Cediranib in combination with olaparib is in clinical development for the treatment of platinum resistant recurrent (PRR) ovarian cancer in patients who have received no more than three prior treatments. Ovarian cancer includes epithelial ovarian cancer (EOC), primary peritoneal cancer and fallopian tube cancer, with EOC being the most common type. Symptoms of ovarian cancer include bloating, pain and frequent urination. Platinum-based chemotherapy is the main type of initial treatment used in ovarian cancer. However, over time some patients may become platinum-resistant whereby this treatment stops working and disease progresses. For these patients, further treatments are needed.

Cediranib works by blocking several specific proteins called the vascular endothelial growth factor (VEGF) receptors that are important in the formation of blood vessels to the tumour. Olaparib is a PARP inhibitor that acts by blocking DNA repair leading to cancer cell death. Olaparib is currently licenced for use in some types of ovarian cancer. If licensed, this combination, taken orally, will offer an option for patients with previously treated ovarian cancer who no longer have a response to platinum therapy and their disease has progressed (PRR).

Proposed Indication

Cediranib in combination with olaparib for previously treated platinum resistant recurrent (PRR) ovarian cancer.[1]

Technology

Description

Cediranib (Cediranib maleate, Recentin; AZD2171) is a quinazoline and a potent adenosine triphosphate (ATP)-competitive inhibitor of VEGF signalling by binding to the intracellular domain of all three VEGF (VEGFR1, VEGFR-2 and VEGFR-3) receptor tyrosine kinases, but mainly through inhibition of the tyrosine kinase of VEGFR-2/Flk-1/KDR. In addition, cediranib significantly inhibits tyrosine kinase activity for c-Kit, the platelet-derived growth factor receptor alpha and beta (PDGFRα and PDGFRβ).[2] Cediranib has been shown to inhibit vessel growth and sprouting *in vitro* and *in vivo*. Cediranib prevents VEGF-induced angiogenesis *in vivo* and shows dose-dependent activity in a range of human tumour xenografts in mice, including colon; lung; prostate; breast; and ovary. Other mechanisms include vascular regression and inhibition of VEGFR-3 mediated lymphangiogenesis.[2-7]

Olaparib (Lynparza; MK-7339, AZD2281) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, PARP-3) 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.[8]

Olaparib in combination with cediranib is in clinical development for the treatment of previously treated PRR ovarian cancer. In a phase II/III trial (NCT02502266, GY-005), olaparib is given twice daily orally and cediranib is given once daily. Both are administered orally at an unspecified dosage.[1]

Key Innovation

Inhibitors of angiogenesis such as cediranib, combined with PARP inhibitors such as olaparib, have demonstrated synergistic effects in treating ovarian cancer in preclinical studies. This synergy has the potential to improve patient outcomes in ovarian cancer.[9,10] If approved, the combination of olaparib and cediranib would be the first recommended treatment in ovarian cancer utilising a combination of angiogenesis inhibitors and PARP inhibitors.

If licensed, cediranib in combination with olaparib will offer an additional treatment option for patients with previously treated PRR ovarian cancer.

Regulatory & Development Status

Olaparib and cediranib in combination do not currently have Marketing Authorisation for any indication in the EU/UK.

Cediranib does not have Marketing Authorisation in the EU/UK for any indication. Olaparib is currently licensed for:[11]

- maintenance treatment of adult patients with advanced (FIGO stages III and IV) Breast Cancer gene 1/2 (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.
- treatment of adult patients with germline *BRCA1/2*-mutations, who have human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer.
- 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
- 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.
- 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

Olaparib in combination with cediranib is currently in phase II/III clinical trials for the treatment of:[12]

- non-small cell lung cancer
- prostate cancer
- recurrent glioblastoma
- solid tumours
- breast cancer

Patient Group

Disease Area and Clinical Need

Ovarian cancer (cancer of the ovaries) mainly affects postmenopausal women (usually over the age of 50).[13] EOC is the most common type of ovarian cancer and starts in the surface layer covering the ovary. The symptoms of ovarian cancer can be very vague and include bloating, a swollen tummy, discomfort in the tummy or pelvic area, feeling full quickly, needing to pee more often, unexplained tiredness, unexplained weight loss, and changes in the bowel habit or symptoms of irritable bowel syndrome.[13,14] Fallopian tube cancer, is another form of ovarian cancer and symptoms can be similar to those of ovarian cancer, and can also include vaginal bleeding unrelated to menstruation and a watery vaginal discharge that may contain blood.[15] Peritoneal cancer is a rare cancer of the peritoneum and is similar to epithelial ovarian cancer. Again, symptoms are unclear and are similar to other conditions: painful and swollen abdomen, constipation or diarrhoea, nausea and vomiting, indigestion, bloating and loss of appetite.[16]

Ovarian cancer is the 6th most common cancer in women in the UK, accounting for 4% of all new cancer cases in females (2016-2018).[17] According to statistical analysis, the incidence rates for ovarian cancer are projected to rise by 15% in the UK between 2014 and 2035, from 28 cases per 100,000 females in 2014 to 32 cases per 100,000 females by 2035.[18] In 2020-21, there were 34,973 admissions (of which 27,658 were day cases) for primary diagnosis of malignant neoplasm of ovary, fallopian tube and peritoneal neoplasms (ICD-10 codes C56.X, C57.0 and C48.2) in England, which resulted in 37,596 finished consultant episodes (FCE) and 45,281 FCE bed days.[19]

Recommended Treatment Options

NICE recommends the following second-line and further treatment options for PRR ovarian cancer:[10]

- Paclitaxel in combination with platinum or as monotherapy
- Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy

Clinical Trial Information

Trial	**GY-005; COCOS;** NCT02502266; A Randomized Phase II/III Study of the Combination of Cediranib and Olaparib Compared to Cediranib or Olaparib Alone, or Standard of Care Chemotherapy in Women With Recurrent Platinum-Resistant or -Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer **Phase II/III –** recruiting **Location(s):** US, Canada, Japan, South Korea and Puerto Rico **Primary Completion Date:** June 2023
Trial Design	Randomised, parallel assignment, open-label, active comparator
Population	N=562; females 18 years and older; patients must have histologically or cytologically confirmed ovarian cancer, peritoneal cancer or fallopian tube cancer and must have a histological diagnosis of either serous or endometrioid cancer based on local histopathological findings; no more than 3 prior treatment regimens (including primary therapy; no more than 1 prior non-platinum based therapy in the platinum-resistant/-refractory setting)
Intervention(s)	• Cediranib orally once a day + olaparib orally twice daily • Cediranib orally once a day • Olaparib orally twice daily
Comparator(s)	• Standard care (chemotherapy)
Outcome(s)	• Progression-free survival (Phase II and Phase III) [Time frame: time from study enrolment to the onset of progression as determined by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST) criteria, or death due to any cause, whichever occurs first, assessed up to 5 years] • Overall survival (OS) (Phase III) [Time frame: time from study enrolment to death due to any cause, assessed up to 5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of cediranib in combination with olaparib was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Lurbinectedin for treating advanced platinum-resistant ovarian cancer [GID-TA10313]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Cositecan for treating platinum or taxane resistant advanced, mucinous, epithelial ovarian cancer [GID-TA10446]. Expected date of issue to be confirmed.
- NICE technology appraisal. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer [TA389]. April 2016.
- NICE clinical guidelines. 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). B14/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 135: Management of epithelial ovarian cancer. 2013. Revised 2018.[20]
- Capoluongo E, *et al.* Guidance Statement on BRCA1/2 Tumour Testing in Ovarian Cancer Patients. 2017.[21]
- Santaballa A, *et al.* SEOM Clinical Guideline in ovarian cancer. 2016.[22]
- National Comprehensive Cancer Network (NCCN). Ovarian cancer, version 1, NCCN clinical practice guidelines in oncology. 2016.[23]

Additional Information

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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.