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HEALTH TECHNOLOGY BRIEFING MARCH 2019

Cediranib in combination with olaparib for recurrent platinum-resistant ovarian cancer – fourth line or greater

NIHRIO ID	26786	**NICE ID**	10158
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trial.

SUMMARY

Cediranib in combination with olaparib is in clinical development for the treatment of patients with recurrent platinum-resistant ovarian cancer who have received at least 3 prior lines of chemotherapy. Ovarian cancer is the most common type of cancer in women and includes epithelial ovarian cancer as the most common type. Other less common types include primary peritoneal cancer and fallopian tube cancer. Platinum-based chemotherapy is the main type of treatment used in ovarian cancer but over time, some patients may become platinum-resistant, which may recur following other lines of treatment.

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 which acts by blocking DNA repair leading to the cancer cell death. Olaparib is currently licenced for use in some types of ovarian cancer. Both cediranib and olaparib are taken orally. The combination has demonstrated the potential to act synergistically to improve long-term outcomes in recurrent ovarian cancer patients who currently have limited options beyond third-line treatment.

PROPOSED INDICATION

Recurrent platinum resistant high-grade serous epithelial ovarian cancer (including fallopian tube and/or primary peritoneal cancer) with no deleterious or suspected deleterious germline BRCA mutation – fourth line or greater.[1]

TECHNOLOGY

DESCRIPTION

Cediranib (Recentin; AZD2171) is a quinazoline and a potent ATP-competitive inhibitor of vascular endothelial growth factor (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]

Poly(ADP-ribose) polymerase (PARP) inhibitors are a class of therapeutic agents that has shown several mechanisms of action including exploiting the DNA repair functions of PARP.[8] 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.[9] Inhibition of base-excision DNA repair by olaparib potentiates the DNA damage and cytotoxicity caused by platinum chemotherapy, leading to an increase in genomic instability and tumour cell death.[10,11]

Cediranib in combination with olaparib is in clinical development for the treatment of patients with recurrent platinum resistant high-grade serous epithelial ovarian cancer (including fallopian tube and/or primary peritoneal cancer) with no deleterious or suspected deleterious germline BRCA mutation who have received at least 3 prior lines of chemotherapy. In the phase IIb clinical trial (CONCERTO; NCT02889900), participants receive oral dose of cediranib tablet 30 mg once daily and olaparib tablet 200 mg twice daily. There is no maximum duration for study treatment, as reported on the trial registry.[1]

INNOVATION AND/OR ADVANTAGES

There has been growing interest in the combination of cediranib and PARP inhibitors. Enhanced PARP inhibition has been shown under hypoxic conditions. In addition, PARP inhibition has been reported to reduce VEGF-induced angiogenesis[12] and increase VEGFR2 phosphorylation which can be reversed by a VEGFR2 inhibitor.[13] Therefore, the dual use of PARP-inhibitors and anti-angiogenic may have a synergistic effect.[14,15]

Cediranib in combination with olaparib have shown efficacy in ovarian cancer throughout several clinical settings. A phase II study demonstrated that the combination of the two drugs increased progression free survival (PFS) in women with recurrent platinum-sensitive ovarian cancer when compared with olaparib alone.[16] The greatest benefit from the combination was observed in wild-type/unknown BRCA patients, therefore suggesting a possible effect of the combination in platinum resistant ovarian cancer which are mainly BRCA proficient tumours.[17]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Cediranib in combination with olaparib does not currently have Marketing Authorisation in the EU/UK for any indication.

Olaparib as monotherapy is licensed in the EU/UK 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.[9]

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.[9]

Cediranib in combination with olaparib is currently in development for the treatment of various types of cancers including: recurrent platinum-sensitive ovarian cancer, endometrial cancer, renal cell cancer, and advanced solid tumours.[18]

PATIENT GROUP

DISEASE BACKGROUND

Ovarian cancer (cancer of the ovaries) is the most common type of cancer in women. It mainly affects postmenopausal women (usually over the age of 50). However, it can also affect young women.[19] Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer. EOC means cancer started in the surface layer covering the ovary. There are various types of EOC of the ovary including serous and endometrioid cancers. Serous EOC is the most common type.[20] If the cancer cells look underdeveloped and nothing like a normal cell, they are known as undifferentiated or high grade. These cancers tend to grow and spread more quickly than low-grade cancers.[21]

The symptoms of ovarian cancer can be very vague. Signs and symptoms of ovarian cancer 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.[19,21]

Fallopian tube cancer is rare - around 1% of the female reproductive system cancers occur in the fallopian tubes. 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.[22]

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.[22]

Women who undergo treatment for or survive ovarian cancer are at risk of several complications that may persist for a long time and negatively impact the quality of life. These include the early onset of menopausal symptoms and gynaecological problems leading to sexual dysfunction. These in turn can lead to psychological symptoms in addition to those caused by a distortion of body image after hysterectomy and abdominal scarring.[23]

CLINICAL NEED AND BURDEN OF DISEASE

Ovarian cancer is the 6th most common cancer in women in the UK, accounting for 4% of all new cancer cases in females as of 2015. 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.[24,25]

Ovarian cancer incidence is strongly related to age, with the highest incidence rates being in older women. In the UK in 2013-2015, on average each year more than a quarter (28%) of new cases were in females aged 75 and over. Age-specific incidence rates rise steadily from around age 30-34 and more steeply from around age 45-49, with a sharp drop in the oldest age groups. The highest rates are in the 75 to 79 age group.[24]

In 2017-2018 were 42,893 admissions (of which 33,239 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 45,944 finished consultant episodes (FCE) and 61,444 FCE bed days.[26]

There are around 4,100 ovarian cancer deaths in the UK every year. Ovarian cancer mortality rates are projected to fall by 37% in the UK between 2014 and 2035, from 15 cases per 100,000 females in 2014 to 10 deaths per 100,000 females in 2035.[25]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for ovarian cancer is dependent on the stage of disease, general health, and current fertility. Most patients undergo a combination of surgery and chemotherapy. The aim of treatment is to cure cancer if possible. If the cancer is too advanced to be cured, treatment aims to relieve symptoms and control cancer for as long as possible.[27]

If performing surgery for women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease.[28] Surgery usually involves removing: both ovaries and the fallopian tubes, the womb (hysterectomy), and/or a layer of fatty tissue in the stomach known as the omentum. Chemotherapy or targeted radiation may also be used in addition to surgery to kill, shrink, and prevent re-growth of cancer cells.[27]

CURRENT TREATMENT OPTIONS

In people who relapse following initial platinum-based therapy, NICE technology appraisal guidance 389 recommends paclitaxel as monotherapy or in combination with platinum, and pegylated liposomal doxorubicin hydrochloride as monotherapy or in combination with platinum, for treating recurrent ovarian cancer.[29]

PLACE OF TECHNOLOGY

If licensed, cediranib in combination with olaparib will offer additional lines of treatment for patients with recurrent platinum resistant high-grade serous epithelial ovarian cancer (including fallopian tube and/or primary peritoneal cancer) with no deleterious or suspected deleterious germline BRCA mutation who have received at least 3 prior lines of chemotherapy.

CLINICAL TRIAL INFORMATION

Trial	CONCERTO, NCT02889900; cediranib in combination with olaparib; phase IIb
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry[1]
Location	United States
Design	Single group assignment, single arm, open label
Participants	n=62; females aged ≥18 years; platinum-resistant relapsed high grade serous, high grade endometrioid or clear cell ovarian, fallopian tube or primary peritoneal carcinoma; at least 3 prior lines of therapy for advanced ovarian cancer; no deleterious or suspected deleterious germline BRCA mutations
Schedule	Subjects receive cediranib 30 mg oral tablet once daily and olaparib 200 mg oral tablet twice daily. There is no maximum duration for study treatment.
Follow-up	Patients should continue on study treatments until objective radiological disease progression, as defined by RECIST version 1.1 guidelines, or they meet other discontinuation criteria. Following discontinuation of study treatment patients will be followed for disease progression (if they have not already progressed), survival and post-progression anti-cancer therapies until the data cut-off for the final overall survival (OS) analysis, approximately 12 months after enrolment of the last patient.
Primary Outcomes	Objective response rate (ORR) by independent central review (ICR), using RECIST version 1.1. [Time Frame: from first patient enrolled to data cut off (8 months after the last patient has received her first dose of IP)]
Secondary Outcomes	• ORR by investigator assessment using RECIST 1.1 [Time Frame: from first patient enrolled to data cut off (8 months after the last patient has received her first dose of IP)] • Duration of response (DoR) assessment using RECIST 1.1 [Time Frame: from first patient enrolled to data cut off (8 months after the last patient has received her first dose of IP)]; • Progression free survival (PFS) assessment using RECIST 1.1 [Time Frame: from first patient enrolled to data cut off (8 months after the last patient has received her first dose of IP)]; • Disease control rate (DCR) assessment using RECIST 1.1 [Time Frame: from first patient enrolled to data cut off (8 months after the last patient has received her first dose of IP)]; • Overall survival (OS) [Time Frame: from first patient enrolled to data cut off (8 months after the last patient has received her first dose of IP)]; • Time to discontinuation or death (TDT) [Time Frame: from first patient enrolled to data cut off (8 months after the last patient has received her first dose of IP)]; • Evaluate quality of life using European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire [Time Frame: from baseline to 30 days after the last dose]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as July 2019.

ESTIMATED COST

The cost of cediranib in combination with olaparib is not known yet.

Olaparib is already marketed in the UK for the treatment of ovarian, fallopian tube, and peritoneal cancers; a pack of 56 x 100 mg or 150 mg tablets costs £2317.50, and a pack of 448 x 50 mg capsules costs £3550.[30]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Lurbinectidin for treating advanced platinum-resistant ovarian cancer (GID-TA10313). Expected publication date to be confirmed
- NICE technology appraisal in development. Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (including a review of technology appraisal no. 381) (GID-TA10303). Expected publication date to be confirmed.
- NICE technology appraisal. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA528). July 2018.
- 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. 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.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer: a national clinical guideline (SIGN 135). Revised in 2018.[31]
- Capoluongo E, et al. Guidance Statement on BRCA1/2 Tumor Testing in Ovarian Cancer Patients. 2017.[32]
- Santaballa A, et al. SEOM Clinical Guideline in ovarian cancer. 2016.[33]
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