Health Technology Briefing
February 2022

Rucaparib maintenance therapy for ovarian, fallopian tube or primary peritoneal cancer after frontline platinum-based chemotherapy

Company/Developer	Clovis Oncology UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33641	NICE ID: 10754	UKPS ID: 664097

Licensing and Market Availability Plans

Currently in phase II/III trials.

Summary

Rucaparib is currently in clinical development for the maintenance treatment of ovarian, fallopian tube, or primary peritoneal cancer, after front-line platinum-based chemotherapy. Epithelial ovarian cancers are the most common type of ovarian cancer. Primary peritoneal cancer and fallopian tube cancer are similar to epithelial ovarian cancer. All three types show signs of pain and swelling in the abdominal area. The optimal treatment strategy for women with newly diagnosed ovarian cancer has yet to be determined.

Rucaparib is a PARP enzyme inhibitor; PARP enzymes play a role in DNA repair in damaged cells, thus inhibiting these enzymes can increase DNA damage and death of cancer cells. PARP inhibitors have demonstrated substantial improvement in progression-free survival as maintenance treatment. Rucaparib will be administered orally. If licensed, rucaparib monotherapy will offer an additional maintenance treatment option for ovarian cancer.

Proposed Indication

Rucaparib maintenance therapy for ovarian, fallopian tube or primary peritoneal cancer after frontline platinum-based chemotherapy.[1]

Technology

Description

Rucaparib (Rubraca, CO-338) is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. *In vitro* studies have shown that rucaparib-induced cytotoxicity involves inhibition of PARP enzymatic activity and the trapping of PARP-DNA complexes resulting in increased DNA damage, apoptosis, and cell death. Rucaparib has been shown to have *in vitro* and *in vivo* anti-tumour activity in Breast Cancer gene (BRCA) mutant cell lines through a mechanism known as synthetic lethality, whereby the loss of two DNA repair pathways is required for cell death. Increased rucaparib-induced cytotoxicity and anti-tumour activity was observed in tumour cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumour growth in mouse xenograft models of human cancer with or without deficiencies in BRCA.[1,2]

Rucaparib monotherapy is in clinical development for maintenance treatment of ovarian, fallopian tube or primary peritoneal cancer after frontline platinum-based chemotherapy (ATHENA, NCT03522246). Rucaparib will be administered orally at a starting dose of 600mg twice a day.[1,3]

Key Innovation

PARP inhibitors have demonstrated substantial improvement in progression-free survival as monotherapy maintenance treatment in the relapsed setting and in the frontline setting for some PARP inhibitors versus active surveillance.[3] In a previous phase III trial (ARIEL3) (NCT01968213), oral rucaparib 600 mg twice daily had an acceptable tolerability profile as maintenance therapy for advanced relapsed ovarian cancer, with a tolerability profile that is generally typical of those of other PARP inhibitors. Rucaparib significantly improved progression-free survival when used as maintenance treatment in patients with platinum-sensitive ovarian cancer. Thus, currently available data indicate that rucaparib is a useful addition to the options available to clinicians for the treatment of advanced ovarian cancer, in maintenance therapy.[4] If licensed, rucaparib monotherapy will offer an additional maintenance treatment option for ovarian cancer within the first line maintenance setting.

Regulatory & Development Status

Rucaparib is currently in licensed in the UK as 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. It is also indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.[2]

Rucaparib monotherapy is currently in phase II and III trials for the treatment of pancreatic cancer, solid tumours, breast cancer, endometrial cancer and clear cell carcinoma.[5]

Patient Group

Disease Area and Clinical Need

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer which can be further classified into different subtypes: serous carcinoma, endometrioid carcinoma, clear-cell carcinoma, mucinous carcinoma, and undifferentiated or unclassified carcinoma. Other types of ovarian cancer include fallopian tube cancer (FTC) and primary peritoneal cancer (PPC). EOC accounts for approximately 90% of all cases of ovarian cancers in the UK.[6] Primary peritoneal cancer is a rare cancer of the peritoneum and fallopian tube cancer starts in the fallopian tubes which connect the ovaries to the womb.[7] Factors that can increase the risk of ovarian cancer includes age - most ovarian cancers develop after menopause- obesity, a family history of ovarian cancer, hereditary conditions (e.g., *BRCA1* and *BRCA2* mutations), fertility treatment, smoking and diet.[8] Signs and symptoms of ovarian, fallopian tube, or peritoneal cancer include pain or swelling in the abdomen, sudden or frequent urge to urinate, trouble eating or feeling full, lump in the pelvic area and gastrointestinal problems, such as gas, bloating, or constipation.[9]

In females in the UK, ovarian cancer is the 6th most common cancer, with around 7,500 new cases every year. 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. More than 71.7% of women diagnosed with ovarian cancer in England survive their disease for one year or more (2013-2017), and more than 42.6% of women diagnosed with ovarian cancer in England survive their disease for five years or more (2013-2017).[10] In England in 2020-2021 there were 34,677 finished consultant episodes (FCEs), and 32,289 hospital admissions with a primary diagnosis of malignant neoplasm of ovary and fallopian tube (ICD-10 code C56-C57), resulting in 41,888 FCE bed days.[11]

Recommended Treatment Options

NICE recommended treatment options for the maintenance treatment of women with advanced ovarian cancer, after first-line chemotherapy includes:[12]

- 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

In England bevacizumab at the unlicensed dose of 7.5 mg/kg is available as front-line maintenance (following induction treatment with carboplatin, paclitaxel and bevacizumab) in certain defined high risk patient groups through a NHS England baseline funding (NHS clinical policy).[13]

Clinical Trial Information

Trial	**ATHENA; NCT03522246; EudraCT - 2017-004557-17;** A Multicenter, Randomized, Double-Blind, Placebo- Controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy **Phase III –** Active, not recruiting **Location(s) –** 14 countries in EU, UK, US, Canada, Australia and Asia **Primary completion date** – December 2024
Trial Design	Randomised, parallel assignment, quadruple-blinded

Population	N = 1000 (planned); newly diagnosed advanced (FIGO stage III-IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer; completed first-line platinum-based chemotherapy and surgery with a response; 18 years and older, female.
Intervention(s)	Oral rucaparib
Comparator(s)	Matched oral placebo
Outcome(s)	Primary Outcome Measures: Investigator assessed Progression-free survival (PFS) [Time Frame: From randomisation until disease progression (up to approximately 7 years)] See trial registry for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Rucaparib is already marketed in the UK for epithelial ovarian, fallopian tube, or primary peritoneal cancer. The cost of the first line maintenance treatment with rucaparib tablets is not yet known.[2,14]

Relevant Guidance

NICE Guidance

- 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 BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA598). August 2019.
- NICE technology appraisal. Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). May 2005.
- NICE clinical guidance. 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. NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- European Society for Medical Oncology. Updated treatment recommendations for newly diagnosed epithelial ovarian carcinoma from the ESMO Clinical Practice Guidelines. October 2021.[15]

- National Comprehensive Cancer Network. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. February 2021.[16]
- Scottish Intercollegiate Guidelines Network. SIGN 135 - Management of epithelial ovarian cancer. October 2018.[17]
- British Gynaecological Cancer Society. British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice. 2017.[18]

Additional Information

ATHENA consists of two independent comparisons (ATHENA-MONO and ATHENA-COMBO). Patients are randomized 4:4:1:1 to the following: oral rucaparib+ intravenous nivolumab (arm A); oral rucaparib + intravenous placebo (arm B); oral placebo+ intravenous nivolumab (arm C); and oral placebo + intravenous placebo (arm D). ATHENA-MONO compares arm B with arm D to evaluate rucaparib monotherapy versus placebo, and ATHENA-COMBO evaluates arm A versus arm B to investigate the effects of rucaparib and nivolumab in combination versus rucaparib monotherapy. ATHENA-MONO and ATHENA-COMBO share a common treatment arm (arm B) but each comparison is independently powered. This briefing relates to ATHENA-MONO.[3]

References

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