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Newcastle University

Health Technology Briefing
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Rucaparib with nivolumab for the maintenance treatment of newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer

Company/Developer	Clovis Oncology UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24123	NICE ID: 24123	UKPS ID: 664963

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Rucaparib in combination with nivolumab is currently in clinical development for the treatment of newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer, following a response to front-line platinum-based chemotherapy. Epithelial ovarian, fallopian tube, and primary peritoneal cancer are all similar types of ovarian cancer. All three types show signs of pain and swelling in the abdominal area. There are currently no combination treatments approved for the maintenance treatment of newly diagnosed ovarian cancer that includes a poly(ADP-ribose) polymerase (PARP) inhibitor in combination with programmed death-1 (PD-1) receptor inhibitor.

Rucaparib is a PARP inhibitor; PARP enzymes play a role in DNA repair, thus inhibition of this has shown increased DNA damage and cell death. Nivolumab is a PD-L1 receptor inhibitor. In preliminary clinical studies, the combination of PARP inhibitor with a PD-1 or PD-L1 inhibitor demonstrated encouraging activity against tumours. Rucaparib will be administered orally with intravenous nivolumab. If licensed, rucaparib in combination with nivolumab will offer an additional maintenance treatment option for newly diagnosed, advanced ovarian cancer.

Proposed Indication

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 in combination with nivolumab is currently in clinical development for the maintenance treatment of newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, following response to front-line platinum-based chemotherapy (ATHENA, NCT03522246). Rucaparib will be administered orally twice daily at a starting dose of 600mg, in combination with intravenous (IV) nivolumab administered once every four weeks at a starting dose of 480mg.[1,3]

Key Innovation

The optimal treatment strategy for women with newly diagnosed ovarian cancer has yet to be determined. PARP inhibitors have demonstrated substantial improvement in progression-free survival as monotherapy maintenance treatment in the frontline setting versus active surveillance. Furthermore, preclinical and early clinical studies have shown that PARP inhibitors and immune checkpoint inhibitors have synergistic antitumour activity and may provide an additional therapeutic option for patients in this population.[3]

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2.[4] Currently, there are no combination therapies recommended by the National Institute for Health and Care Excellence (NICE) for the maintenance treatment of ovarian cancer after frontline therapy that include a PARP inhibitor with a PD-1 inhibitor.[5] Rupacarib is not yet licensed as a combination therapy for any idnication.[2]

In preliminary clinical study results, the combination of a PARP inhibitor with a PD-1 or PD-L1 blocking antibody demonstrated encouraging antitumour activity and a manageable safety profile in patients with ovarian cancer.[6] If licensed, rucaparib in combination with nivolumab will offer an additional maintenance treatment option for newly diagnosed, advanced ovarian cancer.

Regulatory & Development Status

Rupcaraib is currently 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 in combination with nivolumab is currently in phase II and III trials for the treatment small cell lung cancer, leiomyosarcoma, prostate cancer, oesophageal cancer, stomach cancer and gastric cancer.[7]

Patient Group

Disease Area and Clinical Need

Epithelial ovarian cancers start in the cells covering the ovaries and are the most common type of ovarian cancer. Primary peritoneal cancer and fallopian tube cancer are similar to epithelial ovarian cancer and are treated in the same way. 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.[8] 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.[9] 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.[10]

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).[11]

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.[12]

Recommended Treatment Options

NICE recommended treatment option for the maintenance treatment of women with advanced ovarian cancer, after first-line chemotherapy includes:[5]

- 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

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 in combination with IV nivolumab
Comparator(s)	Matched placebo
Outcome(s)	Investigator assessed Progression-free survival (PFS) [Time Frame: From randomisation until disease progression (up to approximately 7 years)]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Rucaparib and nivolumab are already marketed separately in the UK. The cost of the combination treatment is not yet known.[2,13]

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.[14]
- National Comprehensive Cancer Network. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. February 2021.[15]
- Spanish Society of Medical Oncology. SEOM clinical guideline in ovarian cancer (2020). January 2021.[14]
- Scottish Intercollegiate Guidelines Network. SIGN 135 - Management of epithelial ovarian cancer. October 2018.[16]
- British Gynaecological Cancer Society. British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice. 2017.[17]

Additional Information

References

1 ClinicalTrials.gov. *A Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy (ATHENA). Trial ID: NCT03522246.* 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03522246 [Accessed 10th February 2022].

2 Electronic Medicines Compendium. *Rubraca 250mg film-coated tablets.* 2022. Available from: https://www.medicines.org.uk/emc/product/10027/smpc [Accessed 10th February 2022].

3 Monk BJ, Coleman RL, Fujiwara K, Wilson MK, Oza AM, Oaknin A, et al. ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA–MONO) and rucaparib in combination with nivolumab (ATHENA–COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. *International Journal of Gynecologic Cancer*. 2021;31(12):1589. Available from: https://doi.org/10.1136/ijgc-2021-002933.

4 Electronic Medicines Compendium. *OPDIVO 10 mg/mL concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/6888/smpc [Accessed 10th February 2022].

5 NICE Pathways. *Withdrawal of our NICE Pathways service*. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-pathways/we-are-withdrawing-our-nice-pathways-service [Accessed 25th April 2022] (updated).

6 Clovis Oncology. *ATHENA (GOG-3020/ENGOT-ov45): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study of Rucaparib + Nivolumab Following Front-Line Platinum-Based Chemotherapy in Ovarian Cancer.* 2018. Available from: https://clovisoncology.com/media/1119/rucaparib_bmonk_poster_igcs2018.pdf [Accessed 10th February 2022].

7 ClinicalTrials.gov. *rucaparib, nivolumab, Clovis Oncology | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation, Unknown status Studies | Phase 2, 3.* 2022. Available from:

https://clinicaltrials.gov/ct2/results?cond=&term=rucaparib%2C+nivolumab%2C+Clovis+Oncology&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&recrs=m&phase=1&phase=2 [Accessed 10th February 2022].

8 Cancer Research UK. *Epithelial ovarian cancer.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers [Accessed 10th February 2022].

9 American Cancer Society. *Ovarian Cancer Risk Factors.* 2021. Available from: https://www.cancer.org/cancer/ovarian-cancer/causes-risks-prevention/risk-factors.html [Accessed 10th February 2022].

10 National Cancer Institute. *Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®)–Patient Version.* 2021. Available from: https://www.cancer.gov/types/ovarian/patient/ovarian-epithelial-treatment-pdq [Accessed 10th February 2022].

11 Cancer Research UK. *Ovarian cancer statistics.* 2022. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-Two [Accessed 10th February 2022].

12 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21: Diagnosis.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 10th February 2022].

13 British National Formulary. *RUCAPARIB.* 2022. Available from: https://bnf.nice.org.uk/medicinal-forms/rucaparib.html [Accessed 11th March 2022].

14 Redondo A, Guerra E, Manso L, Martin-Lorente C, Martinez-Garcia J, Perez-Fidalgo JA, et al. SEOM clinical guideline in ovarian cancer (2020). *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*. 2021;23(5):961-8. Available from: https://doi.org/10.1007/s12094-020-02545-x.

15 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Barroilhet L, Behbakht K, Berchuck A, et al. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2021 01 Feb. 2021;19(2):191-226. Available from: https://doi.org/10.6004/jnccn.2021.0007.

16 Network SIG. *SIGN 135 - Management of epithelial ovarian cancer.* 2018. Available from: https://www.sign.ac.uk/media/1073/sign135_oct2018.pdf [Accessed 10th February 2022].

17 Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, et al. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. *Eur J Obstet Gynecol Reprod Biol*. 2017;213:123-39. Available from: https://doi.org/10.1016/j.ejogrb.2017.04.016.

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