National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: May 2018

Rucaparib (Rubraca) for platinum-sensitive, high-grade serous or endometrioid epithelial ovarian cancer, primary peritoneal or fallopian tube cancer

NIHRIO (HSRIC) ID: 11936 NICE ID: 8344

LAY SUMMARY

Ovarian cancer is the most common type of cancer in women. It mainly affects old age women but can also affect young women. Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer. Inherited gene mutations (faults) increase the risk for ovarian cancer. Primary peritoneal cancer (PPC) is a rare cancer of the peritoneum (a layer of thin tissue that lines the inside of the tummy and covers all of the organs within it). PPC mainly affects women and it is very similar to EOC. Fallopian tube cancer is a rare cancer of the fallopian tube (tubes that connect the ovaries to the womb).

Rucaparib is a medicinal product under development for the treatment of patients with platinum-sensitive, high-grade serous or endometrioid EOC, primary peritoneal or fallopian tube cancer. Rucaparib has anti-tumour activity by blocking the effect of certain enzymes leading to the death of tumour cells. Rucaparib is given by mouth as tablets. If licensed, rucaparib will offer an additional treatment option for patients with platinum-sensitive relapsed, high-grade serous or endometrioid EOC, primary peritoneal or fallopian tube cancer

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.

TARGET GROUP

Rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer.[1]

TECHNOLOGY

DESCRIPTION

Rucaparib (Rubraca) is an inhibitor of Poly (ADP-ribose) polymerase (PARP) enzymes (PARP-1, PARP-2 and PARP-3). Via an inhibitory effect on the PARP enzymatic activity, rucaparib decreases the formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. It is proposed that PARP inhibition specifically targets tumour cells with pre-existing homologous recombination deficiency (HRD), such as those cells possessing mutations in the BRCA1 or BRCA2 genes. Rucaparib induces synthetic lethality by disrupting single- and double-strand repair pathways leading to tumour cell death. It is also suggested that PARP inhibition can lead to trapping of PARP-1 enzyme on damaged DNA, effectively preventing continuation of the DNA repair process; defective BRCA1 recruitment to damaged DNA; and activation of alternative DNA repair such as error-prone non-homologous end joining (NHEJ) or alternative end joining pathways leading to mutations or chromosomal changes and ultimately cell death.[2]

In the phase III clinical trial (NCT01968213), rucaparib was given as oral tablets (600 mg twice daily) administered with 8 oz (240 mL) of water on an empty stomach or with food; 28-day cycles of treatment. Doses had to be taken as close to 12 hours apart as possible, preferably at the same times every day. Tablets should be swallowed whole.[1, 3]

On 22 March 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product rucaparib (Rubraca), intended for the treatment of relapsed or progressive ovarian cancer (the full indication is: “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”). The most common side effects are fatigue, nausea, creatinine elevations, liver enzymes elevations, vomiting, anaemia, decreased appetite, dysgeusia, diarrhoea, and thrombocytopenia.[4]

Rucaparib is currently in phase III stage of development for the treatment of metastatic castration-resistant prostate cancer and in phase II stage of development for the treatment of recurrent locally advanced or metastatic bladder cancer.[5]

INNOVATION and/or ADVANTAGES

By blocking the activity of PARPs in cancer cells, rucaparib is expected to stop the cancer cells from being able to repair damaged DNA and this eventually leads to the death of the cancer cells, thereby slowing down the growth of the cancer.[6] The benefits of rucaparib are its anti-tumour activity as measured by objective response rate and response duration as well its safety profile.[4] If licensed, rucaparib will offer an additional treatment option for patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer.

DEVELOPER

Clovis Oncology

REGULATORY INFORMATION/ MARKETING PLANS

Rucaparib is a designated orphan drug in the EU for the treatment of ovarian cancer in October 2012.[6]

Rucaparib is a designated orphan drug in the USA for the treatment of ovarian cancer in July 2012.[7]

Rucaparib was designated Breakthrough Therapy for advanced ovarian cancer by FDA in April 2015.[8]

Rucaparib was granted accelerated approval by the FDA for the treatment of advanced ovarian cancer in December 2016.[9]

The FDA has accepted the company's supplemental New Drug Application (sNDA) for rucaparib and granted priority review status to the application with a Prescription Drug User Fee Act (PDUFA) in April 2018.[5]

PATIENT GROUP

BACKGROUND

Ovarian cancer (cancer of the ovaries) is the most common type of cancer in women. It mainly affects postmenopausal women. However, it can also affect young women.[10] Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer. EOC means the 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.[11] 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.[12]

Ovarian cancer may be categorised according to the response to platinum chemotherapy as follows: platinum-sensitive (responds to platinum-based therapy but relapses after 6 months or more); platinum-resistant (relapses within 6 months of completion of platinum-based chemotherapy) and platinum-refractory (does not respond to initial platinum-based chemotherapy). Although a significant percentage of ovarian cancer tumours respond to initial chemotherapy, between 55% and 75% of those tumours that respond recur within 2 years of completing treatment.[13]

The symptoms of ovarian cancer can be very vague. Signs and symptoms of ovarian cancer include bloating, a swollen tummy, discomfort in 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.[10,14]

Inherited gene mutations (faults) increase the risk for ovarian cancer. BRCA1 and BRCA2 are two example genes that raise cancer risk if they become altered (mutated).[15] Women who have a faulty BRCA1 gene have a 40–60% lifetime risk of developing ovarian cancer. Women who have a faulty BRCA2 gene have a 10–30% lifetime risk of developing ovarian cancer. The risk of developing ovarian cancer starts to increase from around the age of 40 for BRCA1 carriers and in the mid-40s for BRCA2 carriers.[16] Other factors that increase the risk for ovarian cancer include getting older, history of breast

cancer, using hormone replacement therapy (HRT), being overweight or tall, having endometriosis, smoking and using talcum powder.[17]

Primary peritoneal cancer (PPC) is a rare cancer of the peritoneum (a layer of thin tissue that lines the inside of the tummy (abdomen) and covers all of the organs within it, such as the bowel and the liver). It mainly affects women and it is very similar to EOC. This is because the lining of the abdomen and the surface of the ovary come from the same tissue when we develop from embryos in the womb. The causes of PPC are unknown. Most cancers are caused by a number of different factors working together. Research suggests that a very small number of PPCs may be linked to the inherited faulty genes BRCA 1 and BRCA 2. These are the same genes that increase the risk of ovarian cancer and breast cancer. Symptoms for PPC can be very unclear and difficult to spot. The symptoms of PPC include a swollen abdomen due to a build-up of fluid, abdominal pain, constipation or diarrhoea, feeling or being sick, indigestion, bloating, and loss of appetite.[18]

Fallopian tube cancer is a rare cancer of the fallopian tube (tubes that link the ovaries to the womb). Some possible risk factors have been suggested for fallopian tube cancer, including a family history of ovarian or breast cancer, and chronic infection. Researchers think that the faulty BRCA gene might cause around 16 out of 100 cancers (16%) of the fallopian tube. The symptoms of fallopian tube cancer are similar to the symptoms of ovarian cancer. They are often quite vague, particularly if the disease is in its early stages. The symptoms might include vaginal bleeding not related to periods, a watery vaginal discharge that may contain blood, abdominal pain which is often colicky, and a swollen abdomen.[19]

Because treatment involves radical surgery and intense courses of chemotherapy, health-related quality of life (HRQOL) is often compromised.[20] Treatment of ovarian cancer can have impacts on patient's feeling such as low self-esteem and depression. Tiredness and weakness can be a problem during treatment.[21]

CLINICAL NEED and BURDEN OF DISEASE

Ovarian cancer was the sixth most common cancer in females in the UK, with around 7,300 cases diagnosed in 2015. It was the sixth most common cause of cancer death in the UK with around 4,200 deaths in 2016. It accounts for 5% of all cancer deaths in females in the UK in 2016. [22] In England in 2016 there were a total of 5,895 newly diagnosed cases of malignant neoplasm of ovary (ICD-10 code: C56).[23] Incidence rates for ovarian cancer in the UK were highest in females aged 75-79 between 2013 and 2015.[22] About 90% of ovarian cancers are epithelial. This equates to 5,305 cases of EOC, based on the number of ovarian cancer cases diagnosed in England in 2016.[11]

The 2016/2017 Hospital Episodes Statistics (HES) Data recorded 39,380 finished consultant episodes (FCEs), 36,667 admissions and 59,041 FCE bed days due to malignant neoplasm of the ovary (ICD-10 code: C56).[24]

There are no exact numbers for how many people get PPC in the UK. Research suggests that between 7 and 15 out of 100 women (7% to 15%) who have advanced ovarian cancer will actually have PPC. It is very rare in men. Most people are over the age of 60 years when they are diagnosed.[18] Fallopian tubes Cancer is rare. Only around 1 in 100 cancers (1%) of the female reproductive system are this type. In England there were 2,210 hospital admissions in 2016-17 and 2,294 FCEs for malignant neoplasm of the fallopian tube (ICD 10: C57.0). For Malignant neoplasm of specified parts of peritoneum (ICD 10: C48.1) there were 976 admissions and 1,059 FCEs and for malignant neoplasm of peritoneum, unspecified (ICD10: C48.2) there were 4,154 admissions and 4,402 FCEs[24]Overall survival

for women diagnosed with ovarian cancer was 70.4% in 2015 in England. This was the third lowest overall survival for women with cancers when calculated by stage at diagnosis.[25]

More than a third (35%) of women diagnosed with ovarian cancer in England and Wales survive their disease for ten years or more (2010-2011). Almost half (46%) of women diagnosed with ovarian cancer in England and Wales survive their disease for five years or more (2010-2011). Almost three-quarters (73%) of women diagnosed with ovarian cancer in England and Wales survive their disease for one year or more (2010-2011).[22]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development Bevacizumab in combination with carboplatin, gemcitabine and paclitaxel for treating the first recurrence of platinum-sensitive advanced ovarian cancer (ID1145). Expected date of issue: TBC.
- NICE technology appraisal in development. Olaparib for maintenance treatment of ovarian, fallopian tube or peritoneal cancer that has a BRCA germline mutation after response to first-line platinum-based chemotherapy (1124). Expected date of issue: TBC.
- 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) (ID1296). Expected date of issue: TBC.
- NICE technology appraisal in development. Lurbinectidin for treating advanced platinum-resistant ovarian cancer (ID1340). Expected date of issue: TBC.
- NICE technology appraisal in development. Ovarian (epithelial), fallopian and peritoneal cancer - pazopanib (maintenance) (ID545). Expected date of issue: TBC.
- NICE technology appraisal guidance. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). April 2016.
- NICE technology appraisal guidance. 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 guidance. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). May 2013.
- NICE technology appraisal guidance. Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer (TA285). May 2013.
- NICE clinical guideline. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE diagnostic guidance. Tests in secondary care to identify people at high risk of ovarian cancer (DG31). November 2017.

NHS ENGLAND and POLICY 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: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice. British Gynaecological Cancer Society. 2017.[26]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer (SIGN publication no. 135). 2013.[27]
- European Society for Medical Oncology (ESMO). Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma: ESMO Clinical Practice Guidelines. 2013.[28]

CURRENT TREATMENT OPTIONS

NHS England indicates that surgery is the standard curative treatment and combines surgical removal of all disease and a staging procedure. Neoadjuvant chemotherapy is used in surgically un-resectable disease and interval surgery employed thereafter depending on the tumour response. Adjuvant chemotherapy is commonly prescribed as determined by the specialist multidisciplinary team following removal of the primary tumour and pathological assessment. Radiotherapy has no primary role in treatment for ovarian cancer. Women who may be at higher genetic risk should be offered referral to a cancer genetics clinic. Prophylactic oophorectomy should be available for women at high risk.[29]

NICE recommends Olaparib within its marketing authorisation as an option for treating adults with relapsed, platinum sensitive ovarian cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum based chemotherapy only if they have had 3 or more courses of platinum based chemotherapy and the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.[30]

EFFICACY and SAFETY

Trial	**ARIEL3,** NCT01968213; **rucaparib vs placebo; phase III**
Sponsor	Clovis Oncology, Inc.
Status	Ongoing
Source of Information	Trial registry,[1] publication[3]
Location	EU (incl. UK), USA, Canada, Australia, Israel and New Zealand.
Design	Randomised, placebo-controlled, double-blind, parallel assignment
Participants	n= 564 ; aged 18 years and older; females; high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer; received ≥2 prior platinum-based treatment regimens including platinum based regimen that must have been administered immediately prior to maintenance therapy in this trial; received no more than 1 non-platinum chemotherapy regimen; must have had at least a 6-month disease-free period following prior treatment with the penultimate platinum-based chemotherapy and achieved a response; for the last chemotherapy course prior to study entry, patients must have received a platinum-based doublet chemotherapy regimen and have achieved a CR or PR (as

	defined by Response Evaluation Criteria in Solid Tumors (RECIST)) and/or a the Gynecological Cancer Intergroup Cancer Antigen-125 (GCIG CA-125) response.
Schedule	Randomised to rucaparib oral tablets 600 mg twice daily administered twice daily with 8 oz (240 mL) of water on an empty stomach or with food; 28-day cycles of treatment; or placebo oral tablets administered twice daily with 8 oz (240 mL) of water on an empty stomach or with food; 28-day cycles of treatment.
Follow-up	Follow-up period: ~3 years Active treatment: the median duration was 8·3 months (interquartile range (IQR) 3·4–16·1)
Primary Outcomes	Disease progression according to RECIST Version 1.1, as assessed by the investigator, or death from any cause (investigator Progression Free Survival or invPFS), in molecularly defined subgroups [Time Frame: Every 12 calendar weeks (within 7 days prior is permitted) after start of treatment until treatment discontinuation due to disease progression. Study data collection expected to last for ~3 years.]
Secondary Outcomes	• Disease progression according to RECIST v1.1, as assessed by Independent Radiology Review (IRR), or death from any cause (irrPFS), in molecularly defined subgroups [Time frame: every 12 calendar weeks (within 7 days prior is permitted) after start of treatment until treatment discontinuation due to disease progression. Study data collection expected to last for ~3 years.] • Time to a specified decrease in the DSR P subscale of the FOSI-18 patient reported outcome questionnaire [Time frame: screening, day 1 of each treatment cycle, treatment discontinuation visit, and 28-day follow-up visit. Study data collection expected to last for ~3 years.] • Time to a specified decrease in the total score of the FOSI-18 patient reported outcome questionnaire [Time frame: screening, day 1 of each treatment cycle, treatment discontinuation visit, and 28-day follow-up visit. Study data collection expected to last for ~3 years.] • Overall Survival (OS) [Time frame: continuously for ~5 years after patient enrols into study.] • Incidence of Adverse Events (AEs), clinical laboratory abnormalities, and dose modifications [Time frame: continuously for ~3 years after patient enrolls into study.] • Individual model parameter estimates of rucaparib and covariates identification (PK) [Time frame: cycle 1 day 15, and cycle 2 day 1, cycle 2 day 15, cycle 4 day 1, and cycle 7 day 1. Study data collection expected to last for ~7 months.]
Key Results	Median progression-free survival in patients with a BRCA-mutant carcinoma was 16·6 months (95% CI 13·4–22·9; 130 [35%] patients) in the rucaparib group versus 5·4 months (3·4–6·7; 66 [35%] patients) in the placebo group (hazard ratio 0·23 [95% CI 0·16–0·34]; p<0·0001). In patients with a homologous recombination deficient carcinoma (236 [63%] vs 118 [62%]), Median progression-free survival was 13·6 months (10·9–16·2) versus 5·4 months (5·1–5·6; 0·32 [0·24–0·42]; p<0·0001). In the intention-to-treat population, it was 10·8 months (8·3–11·4) versus 5·4 months (5·3–5·5; 0·36 [0·30–0·45]; p<0·0001).
Adverse effects (AEs)	Treatment-emergent adverse events of grade 3 or higher in the safety population (372 [99%] patients in the rucaparib group vs 189 [100%] in the placebo group)

	were reported in 209 (56%) patients in the rucaparib group versus 28 (15%) in the placebo group, the most common of which were anaemia or decreased haemoglobin concentration (70 [19%] vs one [1%]) and increased alanine or aspartate aminotransferase concentration (39 [10%] vs none).
Expected reporting date	Primary completion date reported as April 2017

ESTIMATED COST and IMPACT

COST

The cost of rucaparib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] ClinicalTrials.gov. *A study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3): NCT01968213.* Available from: https://clinicaltrials.gov/ct2/show/study/NCT01968213?term=ARIEL3&rank=1 [Accessed 8th May 2018].

[2] DrugBank.ca. *Rucaparib.* Available from: https://www.drugbank.ca/drugs/DB12332 [Accessed 8th May 2018].

[3] Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, Leary A. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet.* 2017 Oct 28;390(10106):1949-61. Available from: http://dx.doi.org.libproxy.ncl.ac.uk/10.1016/S0140-6736(17)32440-6

[4] European Medicines Agency. *EMA/CHMP/723380/2017.* 22nd Mar 2018. Available from: https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-rubraca_en.pdf [Accessed 8th May 2018].

[5] Clovis Oncology. *Rucaparib.* Available from: http://clovisoncology.com/pipeline/rucaparib/ [Accessed 8th May 2018].

[6] European Medicines Agency. *EU/3/12/1049.* Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2012/11/human_orphan_001123.jsp&mid=WC0b01ac058001d12b [Accessed 8th May 2018].

[7] U.S. Food and Drug Administration. *Search orphan drug designations and approvals: rucaparib*. 31st Jul 2012. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=374712 [Accessed 8th May 2018].

[8] Ovarian Cancer Research Fund Alliance. *Rucaparib receives breakthrough therapy designation from FDA.* 14th Apr 2015. Available from: https://ocrfa.org/2015/04/rucaparib-receives-breakthrough-therapy-designation-from-fda/ [Accessed 8th May 2018].

[9] U.S. Food and Drug Administration. *FDA grants accelerated approval to new treatment for advanced ovarian cancer.* 19th Dec 2016. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533873.htm [Accessed 8th May 2018].

[10] NHS Choices. *Ovarian cancer.* 30th Jan 2017. Available from: https://www.nhs.uk/conditions/ovarian-cancer/ [Accessed 8th May 2018].

[11] Cancer Research UK. *Ovarian cancer: types of ovarian cancer.* 31st Mar 2016. Available from: *http://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial* [Accessed 8th May 2018].

[12] Cancer Research UK. *Ovarian cancer: stages and grades.* 30th Nov 2016. Available from: http://www.cancerresearchuk.org/about-cancer/ovarian-cancer/stages-grades/about-stages-and-grades [Accessed 8th May 2018].

[13] National Institute for Health and Care Excellence. Single Technology Appraisal: Bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. Mar2015. Available from: https://www.nice.org.uk/guidance/ta353/documents/ovarian-epithelial-fallopian-tube-peritoneal-cancer-relapsed-platinumresistant-bevacizumab-id684-final-scope-for-consultation-post-referral2 [Accessed 22nd May 2018].

[14] Cancer Research UK. *Ovarian cancer: symptoms of ovarian cancer. 22nd Feb 2018.* Available from: http://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms [Accessed 8th May 2018].

[15] NHS Choices. *Predictive genetic tests for cancer risk genes.* Available from: https://www.nhs.uk/conditions/predictive-genetic-tests-cancer/ [Accessed 8th May 2018].

[16] Royal Marsden: NHS Foundation Trust. *A beginner's guide to BRCA1 and BRCA2.* Available from: https://shared-d7-royalmarsden-public.s3.amazonaws.com/files_trust/s3fs-public/beginners-guide-to-brca1-and-brca2.PDF [Accessed 8th May 2018].

[17] Cancer Research UK. *Ovarian cancer: risks and causes.* 23rd Mar 2016. Available from: http://www.cancerresearchuk.org/about-cancer/ovarian-cancer/risks-causes [Accessed 8th May 2018].

[18] Cancer Research UK. *Primary peritoneal cancer.* 28th Apr 2016. Available from: http://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/primary-peritoneal [Accessed 22nd May 2018].
[19] Cancer Research UK. *Fallopian tube cancer*. 28th Apr 2016. Available from: http://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/fallopian-tube [Accessed 22nd May 2018].
[20] Chase DM, and Wenzel L. Health-related quality of life in ovarian cancer patients and its impact on clinical management. Expert Rev Pharmacoecon Outcomes Res. 2011 Aug; 11(4): 421–431.
[21] Cancer Research UK. *Ovarian cancer: living with ovarian cancer.* Available from: http://www.cancerresearchuk.org/about-cancer/ovarian-cancer/living-with/coping [Accessed 8th May 2018].
[22] Cancer Research UK. *Ovarian cancer: ovarian cancer statistics.* Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-Two [Accessed 8th May 2018].
[23] Office for National Statistics. *Cancer Registration Statistics, England, 2016*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 9th May 2018]
[24] NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17.* Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 23 October 2017]
[25] Office for National Statistics. *Cancer survival in England: adult, stage at diagnosis and childhood – patients followed up to 2016.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/adultstageatdiagnosisandchildhoodpatientsfollowedupto2016 [Accessed 8th May 2018].
[26] Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, Kehoe S, Ledermann J, Morrison J, Naik R, Rolland P. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. *European Journal of Obstetrics and Gynecology and Reproductive Biology.* 2017 Jun 1;213: 123-39. Available from: https://doi.org/10.1016/j.ejogrb.2017.04.016
[27] Scottish Intercollegiate Guidelines Network (SIGN). *Management of epithelial ovarian cancer.* Edinburgh: SIGN; 2013. (SIGN publication no. 135). [November 2013]. Available from: http://www.sign.ac.uk/assets/sign135.pdf [Accessed 8th May 2018].
[28] Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, ESMO Guidelines Working Group. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology.* 2013 Oct 1; 24(suppl_6):vi24-32. Available from: https://doi.org/10.1093/annonc/mdt333
[29] NHS England. *NHS standard contract for complex gynaecology- specialist gynaecological cancers. E10/S/f.* 2013. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2014/04/e10-cancer-gynae-0414.pdf [Accessed 8th May 2018].
[30] National Institute for Health and Care Excellence: technology appraisal guidance. *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. Available from: https://www.nice.org.uk/guidance/ta381/chapter/1-Recommendations [Accessed 8th May 2018].