

HEALTH TECHNOLOGY BRIEFING JULY 2019

Niraparib for advanced ovarian, fallopian tube or primary peritoneal cancer - maintenance therapy

NIHRI ID	26514	NICE ID	10124
Developer/Company	Tesaro Inc	UKPS ID	Not available

Licensing and market availability plans

Currently in phase III clinical trial

SUMMARY

Niraparib as an oral formulation is in clinical development for maintenance therapy in patients with advanced ovarian, fallopian tube or primary peritoneal cancer following response to first-line platinum-based chemotherapy. Ovarian cancer includes a group of tumours that arise from diverse types of tissue contained in the ovary. The most common type of ovarian cancer arises from epithelial cells (the outside layer of cells) on the surface of the ovary, and can often spread from the ovary to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity. Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to epithelial ovarian cancer.

Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. This means it blocks the action of enzymes called PARP-1 and PARP-2 that help to repair damaged DNA in cells when they divide to make new cells. By blocking PARP enzymes, the damaged DNA in cancer cells cannot be repaired, and the cells die. If licensed for this additional indication, niraparib will offer a maintenance treatment option for patients with advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer following response to first-line platinum-based chemotherapy.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Maintenance therapy in patients with advanced ovarian (stage III and IV),^a fallopian tube or primary peritoneal cancer following response to first-line platinum-based chemotherapy.¹

TECHNOLOGY

DESCRIPTION

Niraparib (Zejula, MK-4827) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. In vitro studies, have shown that mechanism of action of niraparib may involve both the inhibition of PARP enzymatic activity and also the increased formation of PARP-DNA complexes, resulting in DNA damage, apoptosis, and cell death.²

Niraparib is currently in phase III clinical development for the maintenance therapy of advanced ovarian, fallopian tube or primary peritoneal cancer following response to first-line platinum-based chemotherapy. In a phase III clinical trial (PRIMA; NCT02655016), participants who had completed first-line platinum-based chemotherapy (neoadjuvant or adjuvant) and had a response (complete or partial) to the chemotherapy, received either niraparib or matching placebo, 300 mg (3 capsules * 100 mg) administered orally once daily continuously over a 28-day cycle.^{1,3,4} A protocol amendment in Feb 2018, reduced the starting dose to 200mg (2 capsules*100mg) in women who were either < 77kg and/or had a baseline platelet count of <150,000 µl. The following patients were eligible based on surgical status:

- Patients with inoperable Stage III and IV disease are eligible
- All Stage IV patients with operable disease are eligible
- Patients with Stage III or IV disease treated with neoadjuvant chemotherapy and interval debulking surgery are eligible;
- Patients with Stage III disease who have visible residual disease after primary debulking surgery are eligible.^a

INNOVATION AND/OR ADVANTAGES

With current treatments offering no chance of cure and with decreasing progression-free survival (PFS) in between lines of platinum-based chemotherapy, the use of maintenance therapy to extend the time that patients are in PFS and therefore extend the time between lines of chemotherapy has become an area of focus in relapsed recurrent ovarian cancer.⁵

Maintenance therapy to delay progression and the potential to re-treat women with chemotherapy has evolved as a new therapeutic approach in ovarian cancer. Therapies targeting the DNA repair pathway as a maintenance strategy has led to the investigation of PARP inhibitors in this indication.⁶

PARP inhibitors were initially developed to potentiate antitumour activity of ionizing radiations and genotoxic agents (platinum, temozolomide and topotecan). Indeed, all PARP is demonstrated in vitro and in vivo radio or chemo potentiation consistent with their ability of inhibiting DNA damage repair.⁷

One of the key DNA repair pathways is a process called homologous recombination and mutations in this pathway lead to patients being termed as having homologous recombination

^a Information provided by Tesaro Inc.

deficiency (HRD). Germline mutations in the BRCA 1/2 genes are the most well-known mechanisms of HRD.⁸ However, ovarian cancer is characterised by the presence of HRD beyond just BRCA mutations.⁶

Niraparib demonstrated activity in the phase III study, ENGOT-OVA16/NOVA, in platinum sensitive recurrent ovarian cancer in patients, irrespective of BRCA mutation and HRD status, as defined using the Myriad® Mychoice test.^{2b}

To date three PARP inhibitors, niraparib, olaparib and rucaparib are all approved by the European Medicines Agency (EMA) - in the maintenance setting for patients with platinum sensitive relapsed ovarian cancer who achieved a complete response or partial response following platinum-based chemotherapy.^{2,9,10}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, niraparib is licensed in the EU/UK for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.²

The most common adverse events ($\geq 10\%$) among patients receiving niraparib monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decrease appetite, nasopharyngitis, diarrhoea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia.²

In addition to maintenance treatment of ovarian cancer, niraparib is currently in phase III clinical development for the first line treatment of non-mucinous epithelial ovarian cancer, in combination with platinum based chemotherapy and dostarlimab.^b

Niraparib is in phase II and III clinical development for the treatment of the following conditions:^b

- Lung neoplasm
- Platinum-resistant ovarian cancer
- Platinum-sensitive ovarian cancer
- Triple negative breast cancer
- HER2+ metastatic breast cancer
- Pancreatic cancer
- Endometrial cancer
- Urothelial carcinoma
- Esophageal cancer, gastric cancer, adenocarcinoma
- Metastatic carcinoma of the cervix
- Advanced melanoma
- DDR deficient neoplasms
- HNSCC
- Advanced Colorectal cancer

In October 2017, niraparib was granted an orphan drug designation in the EU for the treatment of ovarian cancer.¹¹

^b Information provided by Tesaro Inc.

PATIENT GROUP

DISEASE BACKGROUND

Ovarian cancer is the most common type of gynaecological cancer in women. It mainly affects postmenopausal women (usually over the age of 50). However, it can also affect young women.¹² 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 including serous and endometrioid cancers. Serous EOC is the most common type.¹³ 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.¹⁴

The symptoms of ovarian cancer can be very vague and include bloating, abdominal discomfort, feeling full quickly, needing to urinate more often, unexplained tiredness, unexplained weight loss, and changes in the bowel habit. The symptoms can be similar to those seen with irritable bowel syndrome.^{15,16}

Fallopian tube cancer is rare - around 1% of the female reproductive system cancers occur in the fallopian tubes.¹⁷ 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.¹⁸

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.¹⁹

Ovarian cancer survivors 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.²⁰

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 2016. 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.^{21,22}

Ovarian cancer incidence is strongly related to age, with the highest incidence rates being in older women. In the UK in 2014-2016, 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.²³ 55-58% of females with a known stage are diagnosed at a late stage (stage III or IV) compared to 42-45% at an early stage (stage I or II). Between 17% and 21% of females have metastases at diagnosis.²⁴

In 2017-2018 there 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.²⁵

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 2035.²⁶

One-year net survival for ovarian cancer is highest for patients diagnosed at stage I, and lowest for those diagnosed at stage IV, 2014 data for England show. 99% of patients diagnosed at stage I survived their disease for at least one year, versus 51% patients diagnosed at stage IV.²⁷

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

A woman should be referred for urgent assessment from primary care if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids). Tests should be carried out if a woman (especially if 50 or over) reports having any of the following symptoms, among others, on a persistent or frequent basis – particularly more than 12 times per month:^{28,29}

- persistent abdominal distension (women often refer to this as 'bloating')
- feeling full (early satiety) and/or loss of appetite
- pelvic or abdominal pain
- increased urinary urgency and/or frequency

Additional screening for ovarian cancer may include CA125 serum testing and ultrasound scan. CT scans, x-ray, biopsies, or laparoscopies may be needed to confirm or rule out ovarian cancer by a specialist in hospital.³⁰ Treatment for ovarian cancer is dependent on stage of disease, general health, and current fertility. Most patients undergo a combination of surgery and chemotherapy.³¹

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.³¹

CURRENT TREATMENT OPTIONS

NICE recommends olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.³²

PLACE OF TECHNOLOGY

If licensed, niraparib will offer a maintenance treatment option for patients with advanced ovarian cancer, fallopian tube or primary peritoneal cancer following response to first-line platinum-based chemotherapy.

CLINICAL TRIAL INFORMATION

Trial	PRIMA, NCT02655016 , PR-30-5017-C, EudraCT 2015-000952-11 ; aged ≥ 18 years; phase III
Sponsor	Tesaro, Inc

Status	Ongoing
Source of Information	Trial registry; ^{1,4} Journal Article. ³³
Location	EU countries (incl UK), USA and Canada
Design	Randomised, placebo-controlled, double-blind study
Participants	<p>n=620 (planned); aged \geq 18 years; patient must have histologically confirmed, advanced (FIGO stage III or IV) high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first-line platinum based chemotherapy (neoadjuvant or adjuvant); patient must have clinical complete response or partial response following completion of chemotherapy course.</p> <p>Eligibility was also determined by surgical status with the following patients being eligible:</p> <ul style="list-style-type: none"> • Patients with inoperable Stage III and IV disease • All Stage IV patients with operable disease • Patients with Stage III or IV disease treated with neoadjuvant chemotherapy and interval debulking surgery • Patients with Stage III disease who have visible residual disease after primary debulking surgery
Schedule	<p>Participants were randomised to one of the treatment arms:</p> <ol style="list-style-type: none"> 1. Niraparib 300 mg administered orally once daily continuous over a 28-day cycle 2. Matching placebo administered orally once daily continuous during a 28-day cycle <p>Following a protocol amendment in February 2018 The starting dose of study treatment was based upon the patient's baseline body weight or baseline platelet count.^c</p> <ul style="list-style-type: none"> • Patients with a baseline body weight \geq 77 kg and baseline platelet count \geq150,000 μL were administered niraparib 300 mg (3 X 100 mg capsules) or placebo (3 capsules) daily. • Patients with a baseline body weight <77 kg or baseline platelet count <150,000 μL were administered niraparib 200 mg (2 X 100 mg capsules) or placebo (2 capsules) daily
Follow-up	Participants have been followed up from the date of randomised until the date of first documented progression or date of death from any cause, whichever came first.
Primary Outcomes	<ul style="list-style-type: none"> • Progression Free Survival (Time frame: From date of randomisation until the date of first documented progression or date of death from any cause, whichever came first - approximately 15 months)
Secondary Outcomes	<p>Time frame: 48 months</p> <ul style="list-style-type: none"> • Overall survival • Safety and tolerability of niraparib versus placebo as number of participants with treatment-related adverse events as assessed by CTCAE v4.0 • Patient reported outcomes (PROs) • Time to progression on the next anticancer therapy (PFS2)
Key Results	-
Adverse effects (AEs)	Preliminary safety data for patients with \geq 30 days safety data from blinded pooled niraparib and placebo arms has been presented for patients initiated

^c Information provided by Tesaro Inc.

	on 300mg daily (pre-amendment) and patients initiated on an individualised dose (see above) (post-amendment)		
Dosed	Pre-amendment	Post amendment	
N (%)	466	107	
Any TEAE	437 (93.8)	80 (74.8)	
Any related TEAE	385 (82.6)	70 (65.4)	
Any ≥grade 3 TEAE	227 (48.7)	19 (17.8)	
Any serious AE	96 (20.6)	8 (7.5)	
Any grade thrombocytopenia	217 (46.6)	24 (22.4)	
≥Grade 3 thrombocytopenia	143 (30.7)	6 (5.6)	
Any grade anemia	191 (41.0)	12 (11.2)	
≥Grade 3 anemia	77 (16.5)	3 (2.8)	
TEAE leading to end of treatment	26 (5.6)	2 (1.9)	
The interim safety data suggest that niraparib tolerability is improved when dosing is based upon weight and platelet count.			
Expected reporting date	Estimated primary completion date in Feb 2020		

ESTIMATED COST

Niraparib is already marketed in the UK. The NHS indicative price is a pack of 56 x 100 mg capsules costs £4,500.00, a pack of 84 x100 mg capsules costs £6,750.00.³⁴

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (GID-TA10383). Expected publication date: October 2019.
- NICE technology appraisal guidance. 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 (ID1124). Expected publication date: July 2019.

- NICE clinical guideline. Ovarian cancer: recognition and initial management (CG122). April 2011.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. NHS Standard Contract for Complex Gynaecology - Specialist Gynaecological Cancers. E10/S/f. 2013.
- 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

- European Society for Medical Oncology (ESMO) and European Society of Gynaecological Oncology (ESGO). ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. 2019.³⁵
- Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer: A national clinical guideline (SIGN 135). November 2013, revised 2018.³⁶
- National Comprehensive Cancer Network. Ovarian Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. 2016.³⁷

ADDITIONAL INFORMATION

Tesaro Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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