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HEALTH TECHNOLOGY BRIEFING
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Nivolumab for platinum-resistant advanced or recurrent ovarian cancer

NIHRIO ID	9100	**NICE ID**	9398
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	649889

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

SUMMARY

Nivolumab is in development for the treatment of platinum-resistant, advanced or recurrent ovarian cancer. Ovarian cancer is one of the most common types of cancer in women. The symptoms of the disease are vague, including loss of appetite and tummy pain. This can mean that the cancer is often diagnosed when the disease is advanced and more difficult to treat. Most patients have the cancer removed by surgery and also receive chemotherapy, which usually includes platinum-based drugs. However, ovarian cancer often recurs and the platinum-based chemotherapy drugs may be less effective at treating this recurrence. If the cancer recurs within 6 months of the previous treatment, and platinum-based chemotherapy does not work, the disease is called 'platinum resistant'.

Nivolumab works by improving the activity of white blood cells increasing the ability of the immune system to kill cancer cells. Currently patients with platinum resistant or recurrent ovarian cancer have few treatment options and if licensed, nivolumab could be an effective treatment option.

PROPOSED INDICATION

Platinum-resistant, advanced or recurrent ovarian cancer.[1,a]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo) 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. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2]

In the phase III clinical trial (JapicCTI-153004), patients are given nivolumab intravenously.[1]

INNOVATION AND/OR ADVANTAGES

PD-L1 has been shown to accelerate ovarian cancer progression through the induction of host immune-suppression of peripheral cytotoxic $CD8^+$ T cell lymphocytes.[3] Meta-analysis showed that PD-L1 may not be a prognostic factor for ovarian cancer, however, a bioinformatics study showed that PD-L1 expression was significantly associated with worse PFS of ovarian cancer.[4]

Nivolumab has shown prior efficacy and tolerability in early clinical studies, in patients with platinum-resistant ovarian cancer.[5] These findings suggest that nivolumab could be an effective treatment option for this patient group who have few treatment options.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In the UK, nivolumab as monotherapy or in combination with other cancer therapies has the following therapeutic indications:[2]

- As monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- As monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
- As monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.
- As monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.
- In combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.
- As monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

[a] Information provided by Bristol-Myers Squibb on UK PharmaScan

- As monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.
- As monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

The most common side effects with nivolumab (which may affect more than 1 in 10 people) include tiredness, diarrhoea, nausea (feeling sick), rash and itching, pain in joints, muscles and bones, and hypothyroidism (an underactive thyroid gland), most of which are mild to moderate in severity. Nivolumab is also commonly associated with side effects related to the activity of the immune system on body organs. Most will go away with appropriate treatment or on stopping nivolumab.[6]

Nivolumab as monotherapy or in combination with other medicinal products is in phase III or phase II clinical trial for several types of cancers including glioblastoma, hepatocellular carcinoma, renal cell carcinoma and Hodgkin's lymphoma.[7]

PATIENT GROUP

DISEASE BACKGROUND

Ovarian cancer represents a group of tumours that arise from diverse types of tissue contained in the ovary and is classified from stage I to IV. Advanced ovarian cancer falls within stages III and IV. Stage III denotes that the cancer is locally advanced and has spread outside the pelvis into the abdominal cavity. Stage IV denotes that distant metastasis to other body organs such as the liver and lungs has occurred.[8] Epithelial ovarian cancer means the cancer started in the surface layer covering the ovary.[9] Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to ovarian cancer. Most people are diagnosed with advanced stage disease.[8]

The exact cause of ovarian cancer is unknown but risk factors include a family history of breast cancer, being over 50 years of age, hormone replacement therapy (although any increase in risk is likely to be small), endometriosis and being overweight. Common symptoms of ovarian cancer include feeling constantly bloated, a swollen tummy, discomfort in your tummy or pelvic area, feeling full quickly when eating and needing to pee more often than normal.[10]

Fallopian tube cancer is rare - around 1 - 2% of the female reproductive system cancers occur in the fallopian tubes.[11] Symptoms can be similar to those of ovarian cancer, and can also include vaginal bleeding unrelated to menstruation, a watery vaginal discharge that may contain blood, and abdominal pain which is often colicky.[12]

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, bloating and loss of appetite.[13]

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.[14]

CLINICAL NEED AND BURDEN OF DISEASE

There are around 7,500 new ovarian cancer cases in the UK every year (2014 to 2016). In 2016, ovarian cancer was the 6th most common cancer in the UK and accounted for 4% of all new cancer cases. Incidence rates for ovarian cancer in the UK are highest in females aged 75 to 79 years (2014 to 2016).[15] Directly age standardised incidence rate of malignant neoplasm of ovary and other unspecified female genital organs (ICD 10 code: C56 – C57) in England in 2017 were 22.7 per 100,000 females.[16]

Almost 6 in 10 ovarian cancer cases were diagnosed in late stage in England in 2014.[15] In 2016, the number of patients diagnosed with stage III and stage IV ovarian cancer was 1,809 and 1,167 respectively.[17] Incidence rates for ovarian cancer are projected to rise by 15% in the UK between 2014 and 2035, from 28 cases per 100,000 in 2014 to 32 cases per 100,000 females by 2035.[15,18]

There are 4,100 ovarian cancer deaths in the UK annually (2014 to 2016).[15] Mortality rates for ovarian cancer in the UK are highest in females aged 85 to 89 years (2014 to 2016). Mortality rates are projected to fall by 37% in the UK between 2014 and 2035, from about 15 deaths per 100,000 in 2014 to 10 deaths per 100,000 females by 2035.[15,19]

Ovarian cancer survival in England is the highest for women diagnosed under 40 years in the UK (2009 to 2013).[15] One-year and five-year age-standardised survival rates in England (2013 to 2017) for all stages were 71.7% and 42.6% respectively. One-year age-standardised survival rates was 53.8% for women diagnosed at stage 4. Five-year age-standardised survival rate was 13.4% for women diagnosed at stage 4.[20]

Around 1 in 50 females in the UK will be diagnosed with ovarian cancer in their lifetime. About 11% of ovarian cancer cases in the UK are preventable.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main treatments for ovarian cancer are surgery and chemotherapy. Surgery usually involves bilateral salpingo-oophorectomy, total abdominal hysterectomy and omentectomy. Potentially curative surgery requires resection of all macroscopic disease. More commonly the goal is to reduce the diameters of the remaining pieces of tumour tissues to less than 1cm (optimal debulking). Advanced ovarian cancer is also sometimes treated by radiotherapy to shrink the tumour and reduce pain.[21]

CURRENT TREATMENT OPTIONS

Regarding recurrent ovarian cancer, NICE technology appraisal guidance TA389 recommends the following: [22]

- Paclitaxel in combination with platinum or as a monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer
- Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer

For platinum-resistant ovarian cancer, the British Gynaecological Cancer Society (BGCS) recommendations for practice guideline states that there does not appear to be any advantage in using combination therapies, which are associated with higher rates of adverse events. If the patient cannot tolerate chemotherapy and/or symptoms are not requiring a rapid response

to chemotherapy, then hormonal treatment could be an alternative, although evidence for benefit is limited.[23]

PLACE OF TECHNOLOGY

If licensed, nivolumab could be an effective treatment option for platinum-resistant, advanced or recurrent ovarian cancer.

CLINICAL TRIAL INFORMATION

Trial	JapicCTI-153004; **nivolumab vs chemotherapy (liposomal doxorubicin and gemcitabine); phase III**
Sponsor	Ono Pharmaceuticals Co., Ltd
Status	Ongoing
Source of Information	Trial registry[1,24]
Location	Japan
Design	Randomised, open label study
Participants	n=300; aged ⩾20 years old; female; histologically confirmed epithelial ovarian cancers (including fallopian tube and peritoneal cancer); patients with disease progression or recurrence during platinum-based treatment or less than 6 months after the last dose of a platinum agent
Schedule	Participants were randomised to receive either intravenous nivolumab or intravenous liposomal doxorubicin and gemcitabine
Follow-up	Not reported
Primary Outcomes	Overall survival
Secondary Outcomes	Response rate, progression-free survival, disease control rate, quality of life, safety, etc.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as April 2020.

ESTIMATED COST

The NHS indicative price for nivolumab (Opdivo) 100mg/10ml, 240mg/24ml and 40mg/4ml concentrate for solution for infusion vials is £1,097.00, £2,633.00 and £439.00 respectively.[25]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Ovarian, fallopian tube and peritoneal cancer - rucaparib (ID1184). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Avelumab for previously treated platinum-resistant ovarian cancer (ID1497). Expected publication date: TBC.

- NICE technology appraisal guidance in development. Cositecan for treating platinum or taxane resistant advanced, mucinous, epithelial ovarian cancer (ID826). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Mirvetuximab soravtansine for previously treated platinum-resistant FR-alpha positive ovarian cancer (ID1527). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Lurbinectidin for treating advanced platinum-resistant ovarian cancer (ID1340). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Ovarian cancer - vintafolide (with pegylated liposomal doxorubicin) (ID564). Expected publication date: 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. Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). January 2003. Updated May 2005.
- NICE clinical guidelines. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE quality standard. Ovarian cancer (QS18). May 2012.
- NICE interventional procedures guidance. Ultra-radical (extensive) surgery for advanced ovarian cancer (IPG470). November 2013.

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: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network. SIGN 135: Management of epithelial ovarian cancer. 2013. Revised 2018.[26]
- British Gynaecological Cancer Society. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. 2017.[23]
- European Society for Medical Oncology. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2013.[27]
- NICE Evidence summary. Ovarian cancer (advanced): bevacizumab 7.5 mg/kg in combination with paclitaxel and carboplatin for first-line treatment (ESUOM21). October 2013.[28]

ADDITIONAL INFORMATION

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