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Avelumab with or without Pegylated Liposomal Doxorubicin (PLD) for ovarian cancer – second line

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LAY SUMMARY

Ovarian cancer is a common type of cancer arising from different types of ovarian tissue in the female reproductive system. It is the sixth most common cancer in women in the UK. The ovaries are a pair of small organs located in the pelvis and are part of the female reproductive system. Usually women who have been through menopause are more likely to be affected by ovarian cancer. Most cases are caused by gene changes that develop during a woman's life and are not inherited. Treatment of ovarian cancer involves surgery and/or chemotherapy depending on the stage at diagnosis. Most patients with ovarian cancer are diagnosed at an advanced stage and will require chemotherapy. However, most women ultimately relapse and/or become resistant (refractory) to common first-line chemotherapy treatment. Thus, there is a common need in this cancer to consider the use of second-line treatment.

Avelumab is in development for the second-line treatment of ovarian cancer when used either alone or in addition to the chemotherapy drug, Pegylated Liposomal Doxorubicin (PLD). Avelumab acts by preventing cancer cells from switching off T cells (cells of the immune system), which increases the ability of the T cells to kill the cancer cells. It is to be administered as an intravenous infusion. If licensed, avelumab may offer a second-line treatment option for patients with ovarian cancer, whose disease has relapsed or has become refractory after the first treatment.

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TARGET GROUP

Ovarian cancer (platinum resistant, refractory) – as monotherapy or in combination with pegylated liposomal doxorubicin (PLD) – second line

TECHNOLOGY

DESCRIPTION

Avelumab (Bavencio) is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumour T-cell responses. Avelumab has also shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).[1]

Avelumab monotherapy or in combination with pegylated liposomal doxorubicin (PLD) is currently under development for patients with platinum resistant/platinum refractory ovarian cancer. In the phase III clinical trial (JAVELIN Ovarian 200; NCT02580058), subjects receive avelumab monotherapy given as 10mg/kg as a one hour intravenous (IV) infusion every 2 weeks in 4 week cycles or in combination with PLD given as 40 mg/m2 as a one hour IV infusion every 4 weeks in 4 week cycles.[2]

Avelumab is already marketed in the EU as monotherapy for the treatment of metastatic Merkel cell carcinoma. It is most frequently associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of avelumab.[1]

Avelumab is in phase III clinical development globally or in the EU for the following indications:[3,4]

- Gastric cancer
- Gastroesophageal junction carcinomas
- Non-small cell lung cancer
- First line ovarian cancer
- Adjuvant Merkel cell carcinoma
- Renal cell cancer
- Bladder cancer
- Diffuse large B-cell lymphoma
- Health and neck cancer squamous cell carcinoma
- Triple negative breast cancer

It is also in phase II clinical development globally or in the EU for the following indications:[4]

- Merkel cell carcinoma (first line)
- Osteosarcoma
- Glioblastoma multiforme
- Testicular cancer
- Malignant mesothelioma
- Nasopharyngeal cancer

- Human papillomavirus associated cancer
- Endometrial cancer
- Choriocarcinoma
- Neuroendocrine carcinoma
- Acute myeloid leukaemia
- Thymic carcinoma.

INNOVATION and/or ADVANTAGES

Avelumab is thought to specifically bind to PD-L1, preventing the interaction between PD-L1 and the inhibitory T-cell receptor PD-1. PD-L1 blockade with avelumab has the potential to both enhance tumour-specific effector T cell activity and induce antibody-dependent cell-mediated cytotoxicity (ADCC)-mediated lysis of tumour cells, representing a potential unique dual mechanism of action compared with other anti-PD-1/PD-L1 antibodies. With the potential to utilise both adaptive and innate immune mechanisms to destroy cancer cells, avelumab is unique among anti –PD-L1 or anti-PD-1 antibodies.[5] Therefore, if licensed, avelumab will offer an additional treatment option for patients with ovarian cancer.

DEVELOPER

Merck Serono and Pfizer

PATIENT GROUP

BACKGROUND

Ovarian cancer is a common gynaecological cancer, encompassing a range of tumours arising from different types of ovarian tissue. The most common type of ovarian cancer is epithelial, which often spreads to other surfaces within the abdominal cavity, including the fallopian tube and peritoneal cavity.[6] About 90% of ovarian tumours are epithelial, while primary peritoneal and fallopian tube cancers are both rare malignancies; all three cancers are managed in a similar way.[7,8]

The main symptoms of ovarian cancer include feelings of bloating, swollen abdomen, discomfort in the abdominal or pelvic area, loss of appetite and frequent urination. Other symptoms include persistent indigestion, dyspareunia, change in bowel habits, back pain, vaginal bleeding, lethargy and weight loss.[9]

Causes of ovarian cancer include increasing age, family history, hormone replacement therapy and endometriosis. Other factors include being overweight, smoking and using talcum powder.[10]

As treatment involves radical surgery and intense courses of chemotherapy, health-related quality of life is often compromised.[11] If ovarian cancer is identified (and treated) before the cancer has spread outside the ovary (stages IA and IB), the 5-year relative survival rate is 92%. However, only 15% of all ovarian cancers are found at this early stage.[12] Patients with epithelial ovarian cancer are most commonly diagnosed with advanced-stage disease. Responses to chemotherapy are expected in 80% of women who receive standard platinum- and paclitaxel-based treatment, however, the majority of women with advanced ovarian cancer will ultimately relapse and develop drug resistant disease

(refractory). Thus, there is a common need in this cancer to consider the use of second-line treatment options.[13]

CLINICAL NEED and BURDEN OF DISEASE

According to Cancer Research UK, ovarian cancer was the 15th most common cancer in the UK in 2014 and accounted for 2% of all new cases. In females, ovarian cancer was the sixth most common cancer, with around 7,400 cases diagnosed in 2014. It was the 14th most common cause of cancer death in the UK in 2014 and accounts for 5% for all cancer deaths in the UK.[14]

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.[15] There was a steadily decreasing survival rate with increasing stage, but survival for those diagnosed at stage 1 was high (98.1% for 2015).[16] More than a third (35%) of women diagnosed with ovarian cancer in England and Wales survive their disease for ten years or more. Almost half (46%) of women diagnosed with ovarian cancer in England and Wales survive their disease for five years or more, and three-quarters (73%) of women diagnosed with ovarian cancer in England and Wales survive their disease for one year or more.[14]

In 2016-2017 there were 36,667 admissions for malignant neoplasm of the ovary (ICD-10 code: C56) which resulted in recorded 39,380 finished consultant episodes (FCE) 59,041 FCE bed days.[17]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ovarian (epithelial), fallopian and peritoneal cancer - pazopanib (maintenance) [ID545]. 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. Ovarian, fallopian tube and peritoneal cancer - rucaparib [ID1184]. Expected date of issue: TBC.
- 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. Niraparib for ovarian cancer [ID1041]. Expected date of issue: June 2018.
- NICE technology appraisal. 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. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). May 2013.
- NICE technology appraisal. Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer (TA285). May 2013.

- NICE technology appraisal. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). April 2016.
- 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.
- NICE quality standard. Ovarian cancer (QS18). May 2012.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers.E03/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

- Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, Kehoe S, Ledermann J, Morrison J, Naik R, Rolland P, and Sundar S. *British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice.* British Gynaecological Cancer Society (2014)[18]
- European Society for Medical Oncology. ESMO clinical practice guidelines: gynaecological cancers[19]
- Scottish Intercollegiate Guidelines Network. Management of epithelial ovarian cancer - A national clinical guideline (2013)[20]

CURRENT TREATMENT OPTIONS

The main treatment option for ovarian cancer is surgery. It combines surgical removal of all disease and a staging procedure. Neoadjuvant chemotherapy is used in surgically unresectable disease. Thereafter, depending on the tumour response, interval surgery might be employed. Chemotherapy is commonly prescribed as determined by the specialist multidisciplinary team following removal of the primary tumour and pathological assessment.[21]

Greater than 50% of patients with ovarian cancer are diagnosed at an advanced stage. Despite cytoreductive surgery and platinum- and taxane-based chemotherapies, greater than 70% of patients with advanced ovarian cancer who achieve remission ultimately experience relapse. Because there are few effective treatments for these patients, the development of new treatment strategies is urgently required.[22]

The following drugs are recommended by NICE[23]:

- Gemcitabine, in combination with carboplatin, has a UK marketing authorisation for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence‑free interval of at least 6 months after platinum‑based, first‑line therapy
- Paclitaxel has a UK marketing authorisation for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy
- Pegylated liposomal doxorubicin hydrochloride (PLDH) has a UK marketing authorisation for the treatment of advanced ovarian cancer in women for whom a first‑line platinum‑based

chemotherapy regimen has failed. It has been studied in combination with carboplatin for the treatment of platinum sensitive ovarian cancer but this combination does not have a marketing authorisation

- Topotecan has a UK marketing authorisation for the treatment of women with metastatic carcinoma of the ovary after failure of first‑line or subsequent chemotherapy
- Trabectedin has a UK marketing authorisation, in combination with PLDH, for the treatment of women with relapsed platinum‑sensitive ovarian cancer

EFFICACY and SAFETY

Trial	JAVELIN Ovarian 200, NCT02580058, EudraCT-2015-003091-77; avelumab monotherapy or in combination with PLD, versus PLD monotherapy; phase III
Sponsor	Pfizer Ltd
Status	Active, not recruiting
Source of Information	Trial registry[2], Global Data[4]
Location	13 EU countries (incl UK), USA, Australia, Canada, Japan, and other countries
Design	Randomised, active-controlled, open-label
Participants	N= 550; aged 18 and older; • Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer, including malignant mixed Müllerian tumours with high grade serous component. • Platinum resistant/refractory disease, defined as disease progression within 180 days following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum based therapy (refractory), respectively. • Received up to 3 lines of systemic anticancer therapy for platinum sensitive disease, most recently platinum containing, and no prior systemic therapy for platinum resistant disease.
Schedule	Experimental Arm A: avelumab 10 mg/kg will be given as a 1 hour intravenous infusion (IV) every 2 weeks in 4 week cycles Experimental Arm B: avelumab 10 mg/kg will be given as a 1 hour intravenous infusion (IV) every 2 weeks in 4 week cycles, and PLD 40 mg/m2 will be given as a 1 hour IV infusion every 4 weeks in 4 week cycles Active comparator: PLD 40 mg/m2 will be given as a 1 hour IV infusion every 4 weeks in 4 week cycles
Follow-up	Not reported
Primary Outcomes	Overall Survival (OS) measured up to approximately 20 months [Time Frame: randomization up to approximately 20 months] Progression Free Survival (PFS) [Time Frame: randomization up to approximately 20 months]
Secondary Outcomes	Objective Response [Time Frame: Baseline up to approximately 20 months] Progression Free Survival [Time Frame: randomization up to approximately 20 months]

	Duration of Response [Time Frame: first documentation of objective tumour response up to approximately 20 months] Disease Control [Time Frame: Randomization up to approximately 20 months] Ctrough for avelumab [Time Frame: pre dose and at the end of infusion (immediately before the end of avelumab infusion) on Days 1 and 15.] Cmax for avelumab [Time Frame: pre dose and at the end of infusion (immediately before the end of avelumab infusion) on Days 1 and 15.] Cmax for PLD [Time Frame: in the first 12 patients pre dose, immediately prior to end of infusion, and at 2, 6, 24, and 336 hours (Day 15) post start infusion of PLD on Day 1 of next dose.] Volume of distribution for PLD [Time Frame: in the first 12 patients pre dose, immediately prior to end of infusion, and at 2, 6, 24, and 336 hours (Day 15) post start infusion of PLD on Day 1 of next dose.] Clearance for PLD [Time Frame: in the first 12 patients pre dose, immediately prior to end of infusion, and at 2, 6, 24, and 336 hours (Day 15) post start infusion of PLD on Day 1 of next dose.] Area under the concentration time curve for PLD [Time Frame: in the first 12 patients pre dose, immediately prior to end of infusion, and at 2, 6, 24, and 336 hours (Day 15) post start infusion of PLD on Day 1 of next dose.] Incidence of Anti-Drug Antibody [Time Frame: prior to start of avelumab infusion on Day 1 and at end of treatment for up to 24 months.] EORTC QLQ C30 [Time Frame: once a month before dosing, up to 24 months] EORTC QLQ OV28 [Time Frame: once a month before dosing, up to 24 months] FOSI [Time Frame: once a month before dosing, up to 24 months] EuroQoL EQ 5D [Time Frame: once a month before dosing, up to 24 months] Tumour Tissue Biomarkers [Time Frame: Baseline, optional sample at disease progression] Nab (neutralizing antibodies) against avelumab [Time Frame: performed if ADA is positive: prior to start of avelumab infusion on Day 1 and at end of treatment for up to 24 months.]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date March 2018

ESTIMATED COST and IMPACT

COST

Avelumab is already marketed in the UK for the treatment of metastatic Merkel cell carcinoma; a 200 mg vial costs £768 (excluding VAT). The average cost of treatment per patient is £65,086 based on the list price. Costs may vary in different settings because of negotiated procurement discounts.[24]

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

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