Lay summary

Pembrolizumab is a new drug to treat endometrial carcinoma, which is a type of cancer that begins in the womb. The most common symptoms of this cancer are post-menopausal or irregular vaginal bleeding. Pembrolizumab is given straight into the bloodstream, and if licensed for use in the UK, it could improve survival in patients whose first treatment has stopped working.

This briefing is based on information available at the time of research 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.

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**TARGET GROUP**

- Endometrial carcinoma: advanced; excluding sarcomas and mesenchymal tumours – second line following tumour progression or intolerance to other systemic therapies.

**TECHNOLOGY**

**DESCRIPTION**

Pembrolizumab (Keytruda; MK-3475; SCH-900475) is a humanised monoclonal IgG4 antibody with a stabilising sequence alteration in the Fc region, which targets the programmed death-1 (PD1) protein. The PD-1 receptor is a negative regulator of T-cell activity that is involved in the control of T-cell immune responses. Pembrolizumab selectively blocks the interactions of PD-1 with the PD-L1 and PD-L2 ligands. This action potentiates T-cell responses enabling the activation of anti-tumour responses and cancer specific T-cells. In phase II clinical trials, pembrolizumab is administered by intravenous (IV) infusion at 200mg every 3 weeks for up to 35 administrations.

Pembrolizumab is currently licensed in the EU for the treatment of adults with advanced (unresectable or metastatic) melanoma and locally advanced or metastatic non-small cell lung cancer whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Very common (≥10%) reported adverse reactions include: diarrhoea, nausea, rash, pruritus, arthralgia and fatigue.

Pembrolizumab is also in phase III clinical trials for:
- Breast cancer
- Colorectal cancer
- Multiple myeloma
- Hodgkin’s lymphoma
- Liver cancer
- Gastric cancer
- Oesophageal cancer
- Urogenital cancer

Pembrolizumab is in phase II clinical trials for:
- Adrenocortical carcinoma
- Bladder cancer
- Bone cancer
- Diffuse large B cell lymphoma
- Follicular lymphoma
- Glioblastoma
- Merkel cell carcinoma
- Nasopharyngeal cancer
- Non-Hodgkin's lymphoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Recurrent respiratory papilloma
- Soft tissue sarcoma
- Thymoma
INNOVATION and/or ADVANTAGES

If licensed, pembrolizumab will offer an additional treatment option for patients with advanced endometrial carcinoma.

DEVELOPER

Merck Sharp and Dohme Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase II clinical trials.

PATIENT GROUP

BACKGROUND

Endometrial cancer arises from the lining of the uterus (endometrium), with the majority of cases (95%) being adenocarcinomas. Less common types of endometrial cancer include papillary serous carcinoma, carcinosarcoma, and clear cell carcinoma. The most common symptom of endometrial cancer is post-menopausal or irregular vaginal bleeding. Other symptoms may include lower abdominal pain or discomfort, pain during intercourse, and haematuria. The cause of endometrial cancer in most women remains unknown, however there are several risk factors that increase the chance of this cancer developing, such as increasing age, longer exposure to oestrogen (exogenous or endogenous), increased weight, lower physical activity levels, treatment with tamoxifen, and Lynch syndrome, also known as hereditary non-polyposis colorectal cancer. The single greatest risk factor is age, with 99% of cases being diagnosed in women aged over 40 years.

CLINICAL NEED and BURDEN OF DISEASE

Endometrial cancer is the 4th most common cancer among women in the UK, accounting for 5% of all new cases of cancer in females. In 2013, there were 7,442 new cases of endometrial cancer in England representing an incidence of 29 new cases per 100,000 females for the UK as a whole. Approximately 80% of endometrial cancers express luteinising hormone-releasing hormone receptors. In England, most cases of endometrial cancer are diagnosed at an early stage (84% diagnosed at stage I or II); only 5% of females have metastases at diagnosis (stage IV). The 5 year survival rate for endometrial cancer is 80%. In 2014-15, there were 15,069 hospital admissions for malignant neoplasm of endometrium (ICD-10 C54.1), resulting in 33,142 bed days and 15,981 finished consultant episodes. In 2014, there were 1,448 deaths from malignant neoplasm of endometrium in England and Wales.

The population likely to be eligible to receive pembrolizumab for second line treatment of endometrial carcinoma could not be estimated from available published sources.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE interventional procedure guidance. Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer (IPG356). September 2010.

NHS England Policies and Guidance

This topic is relevant to the following Department of Health policy area:


Other Guidance

- Royal College of Obstetricians and Gynaecologists. Management of Endometrial Hyperplasia. 201611.
- European Society for Medical Oncology. Endometrial Cancer: ESMO Clinical Practice Guidelines. 201312.

CURRENT TREATMENT OPTIONS

Endometrial cancer is treated in the first instance by surgery, and then additionally with radiotherapy and/or chemotherapy depending on the stage of disease and relevant risk factors10,13.

Guidelines recommend standard surgical approaches for the different stages of endometrial cancer12:

- Stage I - total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy.
- Stage II - radical hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy.
- Stage III-IV - maximal surgical debulking.

Radiotherapy may be indicated for patients for whom surgery is contraindicated or who have unresectable disease, or as an adjunct to surgical treatment12,13.

Adjuvant chemotherapy is being investigated for patients with stage I endometrial cancer with multiple adverse risk factors, including patient age, high tumour grade, deeper myometrial invasion, lymphovascular space invasion, high risk histological type and high tumour volume14. Adjuvant chemotherapy is usually advised in all patients with stage II–IV disease following surgery12. Current recommended chemotherapy regimens include15:

- Carboplatin (unlicensed for this indication).
Horizon Scanning Research & Intelligence Centre

- Carboplatin with paclitaxel (unlicensed for this indication).
- Carboplatin with paclitaxel, doxorubicin and cyclophosphamide (unlicensed for this indication).

For metastatic and/or relapsed disease, guidelines recommend endocrine therapy or chemotherapy, using the same agents as listed above. Hormonal therapy mainly involves the use of progestational agents, however tamoxifen and aromatase inhibitors are also used\(^\text{12}\). There is a severe lack of randomised data on the use of chemotherapy and or hormone therapy in metastatic endometrial carcinoma. Historically, the presumed toxicity of chemotherapy based treatment in older, less fit and comorbid patients makes it difficult to undertake randomised clinical trials\(^\text{b}\).

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>KEYNOTE-158, MK-3475-158, NCT02628067; pembrolizumab; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Merck Sharp and Dohme Corp.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^\text{1}).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=1,100 (planned); aged ≥18 yrs; advanced, solid tumour of one of the following: anal carcinoma, biliary adenocarcinoma, neuroendocrine tumours, endometrial carcinoma, cervical carcinoma, vulvar carcinoma, small cell lung carcinoma, mesothelioma, thyroid carcinoma, salivary gland carcinoma, any advanced solid tumour except microsatellite instability high colorectal carcinoma; tumour progression or intolerance to previous therapy; radiologically measurable disease; 0 or 1 on Eastern Cooperative Oncology Group (ECOG) performance scale; life expectancy at least 3 months.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Pembrolizumab 200mg IV every 3 weeks for up to 35 administrations.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for up to 2 yrs.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Objective response rate.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>-</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as September 2017.</td>
</tr>
</tbody>
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**ESTIMATED COST and IMPACT**

**COST**

Pembrolizumab is already marketed in the UK for the treatment of melanoma; a 50mg vial costs £1,315. The cost for up to 35 administrations at 200mg each would be £184,000\(^\text{16}\).

**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: new IV treatment option.
- 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:
- None identified

Other Issues

- Clinical uncertainty or other research question identified:
- None identified

REFERENCES