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HEALTH TECHNOLOGY BRIEFING
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Lenvatinib in combination with Pembrolizumab for advanced or recurrent endometrial cancer - First Line

NIHRIO ID	27730	**NICE ID**	10344
Developer/ Company	Eisai Co Ltd Merck Sharp & Dohme Ltd	**UKPS ID**	655875 656321

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

SUMMARY

Lenvatinib in combination with pembrolizumab is in clinical development for the treatment of advanced or recurrent endometrial cancer. Endometrial cancer is the most common form of womb cancer and originates from the lining of the womb (endometrium). The most common symptoms of this cancer are post-menopausal or irregular vaginal bleeding. Standard of care for patients with advanced or recurrent endometrial cancer is chemotherapy; however, there is a need for more effective and tolerable therapies.

Lenvatinib is a tyrosine kinase inhibitor (TKI) that targets several different growth factor receptors including vascular endothelial growth factor (VEGFR) and fibroblast growth factor receptors (FGFR). By blocking these receptors, lenvatinib can reduce tumour growth. Pembrolizumab is a humanised monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and improves the activity of the immune system to kill cancer cells. If licenced, lenvatinib in combination with pembrolizumab will provide a first line systemic treatment for adults with advanced or recurrent endometrial cancer who have few tolerable therapies available.

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 companies for a factual accuracy check. The companies were available to comment.

PROPOSED INDICATION

The first line systemic treatment of advanced or recurrent endometrial carcinoma.[1]

TECHNOLOGY

DESCRIPTION

Lenvatinib (Lenvima) is a multiple receptor tyrosine kinase inhibitor (TKI) with a novel binding mode that selectively inhibits the kinase activities of all vascular endothelial growth factor receptors (VEGFR), in addition to other proangiogenic and oncogenic pathway-related RTKs including all fibroblast growth factor receptors (FGFR), the platelet-derived growth factor (PDGF) receptor PDGFRα, KIT and RET that are involved in tumour proliferation.[2]

Pembrolizumab (Keytruda, MK-3475) is a humanised monoclonal antibody, which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands 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. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to 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.[3]

Lenvatinib in combination with pembrolizumab is in clinical development for the treatment of advanced or recurrent endometrial cancer. The dose proposed in the phase III trial (NCT03884101) for advanced or recurrent endometrial cancer consists of 20mg of lenvatinib administered orally once daily continuously and 200mg of pembrolizumab administered by intravenous infusion on day 1 of each 3 week treatment cycle.[1]

INNOVATION AND/OR ADVANTAGES

First-line standard of care for patients with advanced or recurrent endometrial carcinoma (EC) is paclitaxel and carboplatin chemotherapy; however, there is a need for more effective and tolerable therapies.[4]

Pembrolizumab and lenvatinib are both anti-tumour biological drugs with different mechanisms of action and are approved as monotherapies for several cancer indications in the UK.[2,3] The decision to combine the agents was based on preclinical data, which suggested co-inhibition of VEGF and PD-1 signalling—e.g. the combination of an immune checkpoint inhibitor (pembrolizumab) and simultaneous inhibition of angiogenesis and VEGF-mediated immune suppression (lenvatinib)—could be an efficacious anti-tumour strategy.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The combination of lenvatinib and pembrolizumab does not currently have Marketing Authorisation in the UK for any indication.

Lenvatinib is currently licenced as a monotherapy for:[2]

- treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)
- treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.

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Lenvatinib is currently licenced in combination with:[6]

- everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Very common adverse events (frequency ≥ 1/10) of lenvatinib as monotherapy include: urinary tract infection, thrombocytopenia, leukopenia, neutropenia, hypothyroidism, hypocalcaemia, hypokalaemia, decreased weight and appetite, insomnia, dizziness, headache, dysgeusia, haemorrhage, hypertension, hypotension, dysphonia, diarrhoea, gastrointestinal and abdominal pains, vomiting, nausea, oral inflammation and pain, constipation, dyspepsia, dry mouth, increased blood bilirubin, hypoalbuminaemia, increased alanine aminotransferase, increased aspartate aminotransferase, palmar-plantar erythrodysaesthesia syndrome, rash, alopecia, back pain, , arthralgia, myalgia, pain in extremity, musculoskeletal pain, proteinuria, fatigue, asthenia and peripheral oedema.[2]

Pembrolizumab is currently licenced as a monotherapy for:[3]

- advanced (unresectable or metastatic) melanoma in adults
- adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% tumour proportion score (TPS) and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.
- first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS with no EGFR or ALK positive tumour mutations
- adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10
- recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.
- the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1
- metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

Pembrolizumab is currently licenced in combination with:[3]

- axitinib, for the first-line treatment of advanced renal cell carcinoma in adults
- pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations
- carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults
- platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Very common adverse events (frequency ≥ 1/10) of pembrolizumab as monotherapy include: anaemia, hypothyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea,

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abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema and pyrexia.[3]

Lenvatinib in combination with pembrolizumab is in phase III clinical development for malignant melanoma, hepatocellular carcinoma, renal cell carcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer, gastroesophageal adenocarcinoma, colorectal neoplasms and urothelial carcinoma. This combination is also in phase II clinical development for advanced solid tumours like ovarian, thyroid and breast cancer.[7]

PATIENT GROUP

DISEASE BACKGROUND

Endometrial cancer is the most common type of uterine cancer.[8] Endometrial means that the cancer starts in the lining of the womb, called the endometrium. The majority of cases are adenocarcinomas, less common types of endometrial cancer include uterine serous carcinoma and clear cell carcinomas.[9] The International Federation of Gynecology and Obstetrics (FIGO) system is used to stage endometrial cancer from stage I (cancer confined to the uterus) to stage IV (cancer that has spread to another body organ).[8]

The most common symptom of endometrial cancer is post-menopausal or irregular vaginal bleeding. About 90% of womb cancers are picked up because of this bleeding, which is why womb cancer is so often diagnosed early. Other symptoms may include lower abdominal pain or discomfort, pain during intercourse, and haematuria.[10]

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, treatment with tamoxifen, endometrial hyperplasia, factors relating to menstruation including starting early, late menopause and polycystic ovary syndrome, and Lynch syndrome, also known as hereditary non-polyposis colorectal cancer. The risk of womb cancer increases with age, almost three quarters of cases of womb cancer are in women aged 40 to 74. Most women diagnosed with womb cancer have had their menopause.[11]

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.[12] In 2018, there were 8,130 registrations of newly diagnosed endometrial cancer in England, an increase of 29% compared with 2008.[13]

In England, most cases of uterine cancer, of which endometrial cancer is the most common type, are diagnosed at an early stage, with about 18-19% being diagnosed at stage III or IV. Between 7% and 8% of uterine cancer patients have metastases at diagnosis (stage IV).[12]

The 5 year survival rate for advanced endometrial cancer, stage III and IV, is approximately 50% and 15% respectively.[14]

In England in 2019-20, there were 16,388 hospital admissions for malignant neoplasm of endometrium (ICD-10 C54.1), resulting in 30,111 bed days and 17,536 finished consultant episodes.[15] In 2019, there were 1,704 deaths from malignant neoplasm of endometrium in England and Wales.[16]

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PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Endometrial cancer is treated in the first instance by surgery to remove the uterus (hysterectomy). This surgery can be more extensive in later stages and by stage IV no longer has a curative aim, referred to as debulking surgery. Younger women who have not already reached the menopause may not want to have their womb and ovaries removed if they wish to have children. In this case, it may be possible under very specific circumstances, to treat the cancer using hormone therapy to reduce tumour size and control symptoms. Additionally, radiotherapy or chemotherapy may be used in the adjuvant setting to reduce the chance of the cancer returning.[17] Chemotherapy is also a systemic treatment for advanced womb cancer.[18]

CURRENT TREATMENT OPTIONS

There are currently no NICE recommended first line medicinal therapies for advanced or recurrent endometrial cancer or a NICE pathway for the disease.[19]

The current British Gynaecological Cancer Society (BGCS) guidelines for endometrial cancer recommend chemotherapy-naïve patients who relapse with systemic disease or those with late relapse after receiving adjuvant chemotherapy, should be considered for doublet chemotherapy with carboplatin and paclitaxel.[20] For metastatic and/or relapsed disease, European Society for Medical Oncology (ESMO) guidelines recommend endocrine therapy or cytotoxic chemotherapy. Hormonal therapy mainly involves the use of progestational agents, however tamoxifen and aromatase inhibitors are also used.[21]

PLACE OF TECHNOLOGY

If licenced, lenvatinib in combination with pembrolizumab will provide a first line systemic treatment for adults with advanced or recurrent endometrial cancer who have few effective, tolerable therapies available.

CLINICAL TRIAL INFORMATION

Trial	**LEAP-001;** NCT03884101, 2018-003009-24; A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001) **Phase III** - Active, not recruiting **Location(s):** EU countries (inc UK), Canada, United states and other countries. **Primary completion date:** April 2023
Trial design	Parallel assignment, randomised, open-label,
Population	N = 875 (estimate), Stage III, Stage IV, or recurrent, histologically-confirmed endometrial carcinoma, females aged 18 years and older.
Intervention(s)	Lenvatinib 20mg administered orally once daily continuously and pembrolizumab administered as a 200mg IV infusion once on day 1 of each 3-week treatment cycle. Participants receive up to 35 infusions of pembrolizumab and should continue with lenvatinib alone thereafter until disease progression or development of unacceptable toxicity.

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Comparator(s)	Paclitaxel 175 mg/m^2 and carboplatin 10 mg/mL (AUC 6) IV infusions once on day 1 of each 3-week treatment cycle. Participants receive up to 7 cycles of paclitaxel plus carboplatin.
Outcome(s)	Primary outcome(s); • Progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ [Time Frame: Up to approximately 31 months] • Overall Survival (OS) [Time Frame: Up to approximately 45 months] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Lenvatinib is already marketed in the UK. The NHS indicative price for 4 mg and 10 mg capsules (30 units) is £1,437.[22]

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[23]

- A 100 mg/4 ml concentrate for solution for infusion vial costs £2,630.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guidelines. Suspected cancer: recognition and referral (NG12). January 2021.
- NICE interventional procedure guidance. Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer (IPG356). September 2010.
- NICE interventional procedure guidance. Laparoscopic techniques for hysterectomy [IPG239]. November 2007.
- NICE diagnostic guidance. Testing strategies for Lynch syndrome in people with endometrial cancer (DG42). October 2020.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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.
- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology: specialist gynaecological cancers. E10/S/f.

OTHER GUIDANCE

- British Gynaecological Cancer Society. BGCS Uterine Cancer Guidelines: Recommendations for Practice. 2017.[20]

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ADDITIONAL INFORMATION

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