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Newcastle University

Health Technology Briefing
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Pembrolizumab with chemotherapy for treating advanced or recurrent endometrial cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 37144	NICE ID: Not available	UKPS ID: 669633

Licensing and Market Availability Plans

Currently in phase 3 clinical trials, with primary results published.

Summary

Pembrolizumab with carboplatin and paclitaxel is in development for the treatment of endometrial cancer (cancer of the womb lining) when it has started to spread to other parts of the body (advanced) or has come back after initial treatment (recurrent). Symptoms of endometrial cancer can include abnormal vaginal bleeding, pelvic pain, painful urination or pain during sex. Cancer that recurs or has spread is harder to treat, and the aim of treatment is usually to control symptoms and if possible, limit cancer progression. There is a need for treatments that provide longer-lasting positive outcomes for women with advanced or recurrent endometrial cancer.

Pembrolizumab is a type of targeted therapy given intravenously, that works with the immune system to fight cancer (immunotherapy). Currently used in the UK to treat several types of cancer, it is a protein similar to the immune system's natural antibodies that has been designed to recognise and block a receptor (or 'target') named PD-1. PD-1 can switch off the immune system's response to a cancer, so by blocking PD-1, pembrolizumab helps the immune system to stay active and destroy cancer cells. If licenced, pembrolizumab with carboplatin and paclitaxel will provide a new targeted immunotherapy option for patients with advanced or recurrent endometrial cancer.

Proposed Indication

Pembrolizumab in combination with chemotherapy for the treatment of patients with advanced or recurrent endometrial cancer.[1]

Technology

Description

Pembrolizumab (Keytruda) is a type of targeted therapy drug called an immune checkpoint inhibitor (a type of immunotherapy).[2] It 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. These ligands are expressed in antigen-presenting cells and additionally may be expressed by tumour cells. The PD-1 receptor is expressed on the surface of activated T-cells and has been shown to be involved in the control (negative regulation) of T-cell immune responses.[3,4] Through blockade of PD-1 binding to ligands PD-L1 and PD-L2, pembrolizumab potentiates T-cell responses, including anti-tumour responses.[4]

Pembrolizumab in combination with paclitaxel and carboplatin, then continued in a maintenance treatment phase, is in clinical development for the treatment of stage 3, 4A or 4B or recurrent endometrial cancer.[1]

In the phase III clinical trial (NCT03914612) patients are administered pembrolizumab via intravenous infusion (IV) with paclitaxel IV and carboplatin IV for 6 to 10 three-week cycles depending on response to treatment. This is followed by maintenance treatment with pembrolizumab IV on day 1 of each cycle, which repeats every 6 weeks up to 14 cycles, for a total of 20 cycles of pembrolizumab in the combination and maintenance phases.[1,5]

Key Innovation

There is an unmet need for treatments for advanced endometrial cancer with improved progression free outcomes as the 5-year overall survival rate for patients with advanced or recurrent disease is less than 20%.[6] Uterine cancer (around 90% of which are endometrial cancer) is one of only a few malignant conditions for which both incidence and mortality are currently rising.[7,5]

The combination of pembrolizumab and cytotoxic chemotherapy has resulted in clinically significant improvements in progression-free and overall survival in patients with multiple types of solid tumours. It has been hypothesised that this combination can be an effective treatment due to increased antigenic diversity in tumours from failure to repair point mutations and the potential immunogenic effects of the cytotoxic chemotherapy.[5]

If licenced, pembrolizumab in combination with paclitaxel plus carboplatin will provide a new targeted immunotherapy combination for the treatment of patients with advanced or recurrent endometrial cancer.

Regulatory & Development Status

Pembrolizumab in combination with paclitaxel and carboplatin currently has Marketing Authorisation in the UK for the first line treatment of metastatic, squamous non-small cell lung cancer (NSCLC) in adults.[4]

Pembrolizumab is currently marketed in the EU/UK in combination with other medicinal products for the following indications:[4]

- NSCLC
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Oesophageal carcinoma

- Triple-negative breast cancer
- Endometrial carcinoma
- Cervical cancer

Pembrolizumab is also currently marketed in the EU/UK as a monotherapy for the following indications:[4]

- Endometrial carcinoma: microsatellite instability high (MSI-H) or dMMR, advanced or recurrent and progressing on or after platinum containing therapy in any setting and who are not candidates for curative surgery or radiation.
- Melanoma
- NSCLC
- Urothelial carcinoma
- Classical Hodgkin lymphoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Colorectal cancer (MSI-H or dMMR)
- Gastric cancer (MSI-H or dMMR)
- Small intestine cancer (MSI-H or dMMR)
- Biliary cancer (MSI-H or dMMR)

Pembrolizumab in combination with paclitaxel and carboplatin is currently in phase II and III clinical trials for multiple indications, including but not limited to:[8]

- Triple negative breast cancer
- Recurrent/metastatic head and neck squamous cell carcinoma
- Metastatic melanoma
- Advanced or recurrent non-small cell lung cancer
- Cervical cancer
- Ovarian, primary peritoneal or fallopian tube cancer
- Oesophageal adenocarcinoma

Patient Group

Disease Area and Clinical Need

Endometrial cancer, which can also be described as womb or uterine cancer, is cancer that started in the lining of the womb (endometrium).[9] Removal of the whole womb is a curative option at early stages of disease.[10] Advanced cancer refers to cancer that has spread from the womb lining into the surrounding tissues or beyond; it cannot usually be cured.[11,12] Stage 3 endometrial cancer is when it has spread outside of the uterus, this may include pelvic or para-aortic lymph nodes. Stage 4A refers to cancers that have grown into the bladder and/or bowel, and stage 4B cancers have spread to other lymph nodes, or the liver, lungs, omentum, or other organs.[13] Recurrent cancer means cancer that has returned after primary treatment.[11] The most common symptom of endometrial cancer is abnormal vaginal bleeding.[9] Other symptoms of endometrial cancer can include swelling in the tummy or pelvis, pain in the pelvis or lower

back, or during sex, or blood in the urine.[14] Risk factors for endometrial cancer are known to include increasing age (with most cases occurring in women aged between 40 and 74 years old), early puberty and/or late menopause, having diabetes or being overweight or obese, having polycystic ovary syndrome or a previous history of taking tamoxifen (breast cancer medication).[15]

Endometrial cancer is the 4th most common cancer among women in the UK.[15] In England, there were 8,051 new cases per year, averaged across 2016 to 2018.[16] The age-standardised incidence rate in England for endometrial cancer (2016-2018) was 29.5 per 100,000 females.[16] In England, for diagnoses between 2013-2017, the age-standardised average 5-year net survival rate for advanced uterine cancer was almost 50% at stage 3 but only 15% at stage 4.[17] Endometrial cancers account for the majority of uterine cancer cases.[7] From 2017-2019 in England, the age standardised mortality rate of endometrial cancer per 100,000 female population was 7.0 in England.[18] In England (2022-23), there were 18,945 finished consultant episodes (FCE) and 17,713 admissions for endometrial cancer (ICD-10 code C541) which resulted in 29,419 FCE bed days and 9,996 day cases.[19]

Recommended Treatment Options

NICE currently recommends the following therapies for the treatment of previously treated endometrial cancer:

- Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer.[20]
- Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency.[21]
- Pembrolizumab for advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency that has progressed during or after a platinum-based therapy, in adults who cannot have curative surgery or radiotherapy.[22]

There is currently no treatment option recommended by NICE for previously untreated endometrial cancer.

Clinical Trial Information

Trial	NCT03914612; A Phase III Randomized, Placebo-Controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer **Phase III** – Active, not recruiting **Locations:** USA, Canada, Japan, Republic of Korea and Puerto Rico. **Primary completion date:** December 2022.
Trial Design	Randomized, placebo-controlled, parallel assignment, quadruple blinded.
Population	N=816 (actual); female adults (18 years and older) with endometrial cancer that is: Measurable (by RECIST v 1.1) stage 3; measurable stage 4A; stage 4B with or without measurable disease, or recurrent with or without measurable disease.[5] • Patients may have received no prior chemotherapy for endometrial cancer. For recurrent cancer, any previous adjuvant chemotherapy must have been completed at least a full year prior to Step 2 registration. • Patients may have received prior radiation therapy for treatment of endometrial cancer, which must have been completed at least 4 weeks prior to Step 2 registration.

	• Patients may have received prior hormonal therapy for treatment of endometrial cancer. All hormonal therapy must be discontinued at least three weeks prior to Step 2 registration.
Intervention(s)	• Combination phase: Pembrolizumab IV with IV paclitaxel and IV carboplatin; every 3 weeks for 6 cycles and up to 10 cycles where at 6 cycles measurable disease is assessed as stable disease or partial response using RECIST criteria.[5] • Maintenance phase: Pembrolizumab IV every 6 weeks to a maximum total of 20 cycles across both combination and maintenance phases.[5]
Comparator(s)	• Combination phase: placebo IV with IV paclitaxel and IV carboplatin; every 3 weeks for 6 cycles and up to 10 cycles where at 6 cycles there is measurable disease assessed as stable disease or partial response using RECIST criteria.[5] • Maintenance phase: placebo IV every 6 weeks to a maximum total of 20 cycles across both combination and maintenance phases.[5]
Outcome(s)	**Primary outcome measure:** • Progression-free survival (PFS) [Time Frame: assessed up to 5 years.] See trial record for full list of other outcomes.
Results (efficacy)	Efficacy was assessed separately for dMMR and pMMR tumours. Kaplan–Meier estimates of PFS in the dMMR cohort were 74% in the pembrolizumab group at 12 months, compared with 38% in the placebo group (hazard ratio for progression or death, 0.30; 95% confidence interval [CI], 0.19 to 0.48; P<0.001), reflecting a 70% difference in relative risk. In the pMMR cohort, median PFS was 13.1 months with pembrolizumab and 8.7 months with placebo (hazard ratio, 0.54; 95% CI, 0.41 to 0.71; P<0.001).[5] The addition of pembrolizumab to standard chemotherapy (paclitaxel plus carboplatin), followed by pembrolizumab maintenance, resulted in a 70% lower risk of disease progression or death in the mismatch repair-deficient disease (dMMR) cohort and a 46% lower risk in the mismatch repair-proficient disease (pMMR) cohort than in the placebo group. The median follow up was 12 months in dMMR cohort and 7.9 months in pMMR. These data suggest that the incorporation of immunotherapy into the first-line treatment of patients with advanced or recurrent endometrial cancer translates into improved oncologic outcomes, regardless of MMR status.[5]
Results (safety)	Adverse events were as expected for pembrolizumab and combination chemotherapy. Common adverse events were fatigue, peripheral sensory neuropathy, anaemia, nausea, constipation, diarrhoea, thrombocytopenia, arthralgia, dyspnea, myalgia, neutropenia, vomiting, weight loss or rash. Less common adverse events with a possible immune-related cause were infusion reaction, hypo- or hyperthyroidism, colitis, pneumonitis, glucose intolerance, acute kidney injury, hepatic failure, myositis, hypophysitis, pancreatitis and adrenal insufficiency.[5]

Estimated Cost

Pembrolizumab is already marketed in the UK; the NHS indicative price (hospital only) of one 100mg/4ml vial of concentrate for solution for infusion is £2,630.[23]

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Durvalumab for maintenance treatment of recurrent or advanced endometrial cancer (GID-TA11340). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Niraparib with dostarlimab for maintenance treatment of advanced or recurrent endometrial cancer (GID-TA11365). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Lenvatinib with pembrolizumab for untreated recurrent or advanced endometrial cancer (GID-TA10851). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Endometrial cancer (high risk, newly diagnosed) - pembrolizumab (with chemotherapy, adjuvant) (GID-TA11235). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Dostarlimab with platinum-containing chemotherapy for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (GID-TA10850). Expected publication date February 2024.
- NICE technology appraisal. Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency (TA914). September 2023.
- NICE technology appraisal. Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer (TA904). June 2023.
- NICE technology appraisal. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779). March 2022
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015. Last updated: August 2023.

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). B14/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). Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2022.[24]
- Spanish Society of Medical Oncology. SEOM-GEICO clinical guidelines for endometrial cancer (2021). 2022.[25]
- British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice. 2021.[26]
- European Society of Gynaecological Oncology (ESGO). ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. 2021.[27]

Additional Information

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