NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
October 2022

Pembrolizumab and chemotherapy with or without radiotherapy as an adjuvant therapy for treating newly diagnosed high-risk endometrial cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30818	NICE ID: 11808	UKPS ID: 661793

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab in combination with chemotherapy with or without radiotherapy is currently in clinical development for the treatment of newly diagnosed high-risk endometrial cancer after surgery (adjuvant therapy). 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. Women with high-risk endometrial cancer are at increased risk of recurrence and disease progression following surgery. Current adjuvant therapy options include chemotherapy and/or radiotherapy, but there is a need for additional treatment options to improve outcomes. There are currently few targeted treatments available for this patient population.

Pembrolizumab, administered intravenously, is a type of therapy that stimulates the body's immune system (immunotherapy) by triggering immune cells called T-cells to find and kill cancer cells. Pembrolizumab is a monoclonal antibody, a protein that has been designed to recognise and block a receptor ('target') called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system (the body's natural defences), preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. If licensed, pembrolizumab in combination with adjuvant chemotherapy with or without radiotherapy would provide an additional targeted treatment option for patients with newly diagnosed high-risk endometrial cancer.

Proposed Indication

Pembrolizumab in combination with adjuvant chemotherapy with or without radiotherapy for the treatment of newly diagnosed high-risk endometrial cancer after surgery with curative intent.[1]

Technology

Description

Pembrolizumab (Keytruda) 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.[2]

Pembrolizumab in combination with adjuvant chemotherapy with or without radiotherapy is currently in phase III clinical development for the treatment of newly diagnosed high-risk endometrial cancer after surgery with curative intent. In the phase III trial, KEYNOTE-B21 (NCT04634877), pembrolizumab 200mg will be administered every three weeks (Q3W) via intravenous infusion (IV) for 6 cycles, followed by pembrolizumab 400mg IV every six weeks (Q6W) for an additional 6 cycles. During the Q3W dosing period of pembrolizumab, participants receive concurrent standard of care chemotherapy for 4 or 6 cycles. At the investigator's discretion, participants optionally receive radiotherapy starting within 6 weeks of completion of standard of care chemotherapy.[1]

Key Innovation

Although women with endometrial cancer generally have a favourable prognosis, those with high-risk disease features are at increased risk of recurrence. Women with high-risk endometrial cancer are at increased risk of distant metastases and cancer-related death. Pelvic external beam radiotherapy has been the standard adjuvant treatment for women with high-risk endometrial cancer for many decades, although there is a paucity of evidence on improvement of survival. Randomised trials have compared adjuvant chemotherapy with external beam radiotherapy. Radiotherapy was shown to delay pelvic recurrence and chemotherapy was shown to delay distant metastases, but no differences in survival were found.[3]

Tailored therapy (with immunotherapy agents such as pembrolizumab) according to the molecular characterisation is expected to be one of the drivers to improve the outcomes across solid tumours in endometrial cancer.[4]

If licensed, pembrolizumab in combination with adjuvant chemotherapy with or without radiotherapy would provide an additional targeted treatment option for patients with newly diagnosed high-risk endometrial cancer.

Regulatory & Development Status

Pembrolizumab as a monotherapy and in combination with various other medicinal products is approved for the treatment of a number of different cancer indications, including:[2,5,6]

- Non-small cell lung cancer
- Renal cell carcinoma
- Triple-negative breast cancer
- Endometrial carcinoma

- Melanoma
- Classical Hodgkin lymphoma
- Head and neck squamous cell carcinoma
- Colorectal cancer
- Oesophageal cancer
- Urothelial cancer
- Cervical cancer
- Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers (colorectal, endometrial, gastric, small intestine, biliary cancer)

Pembrolizumab as a monotherapy or in combination with various other medicinal products is being developed for several indications in phase II and phase III clinical trials, some of which include:[7]

- Hepatocellular carcinoma (HCC)
- Bladder cancer
- Ovarian cancer
- Prostate cancer

Patient Group

Disease Area and Clinical Need

The most common type of womb cancer is endometrial cancer. Endometrial means that the cancer starts in the lining of the womb, the endometrium. Carcinoma means that the cancer has started in a surface or lining layer of cells (the epithelium). Carcinosarcoma is a rare type of womb cancer. It has features of both endometrial cancer and sarcoma and is generally faster growing and more likely to spread in comparison to some other types of endometrial cancer.[8] The exact cause of endometrial cancer is not known but there are risk factors that are known. These include older age, being overweight, higher oestrogen levels, hormone replacement therapy, tamoxifen, diabetes, polycystic ovary syndrome and having a family history of womb cancer.[9] The most common symptom of womb cancer is abnormal bleeding from the vagina, especially in post-menopausal women. Less common symptoms include haematuria, anaemia, thrombocytosis and high blood sugar levels.[10] High risk endometrial cancer includes those with one or more defined clinical or pathological risk factors for recurrence or mortality.[11]

Womb cancer is the 4th most common cancer in females in the UK, accounting for 5% of all new cancer cases in females (2016-2018). Womb cancer accounts for 3% of all new cancer cases in males and females combined.[12] The age standardised incidence rate of womb cancer in England was 29.5 per 100,000 amongst females (2016-2018).[13] In England (2020-21), there were 16,020 finished consultant episodes (FCEs) and 14,958 admissions for malignant neoplasm: endometrium (ICD-10 code C54.1), which resulted in 7,381 day cases and 23,997 FCE bed days.[14] In England (2017), there were 7,732 patients diagnosed with malignant neoplasm of corpus uteri and 1,540 deaths registered where malignant neoplasm of corpus uteri was the underlying cause.[15] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for uterine cancer were 89.5% and 75.6% respectively.[16]

Recommended Treatment Options

Treatment for endometrial cancer usually involves surgery, chemotherapy or radiotherapy. It may also include treatment with targeted medicines to treat the cancer.[17] Treatment for high risk womb cancer involves surgery to remove the womb, fallopian tubes and ovaries (hysterectomy). After surgery, patients may also have one of the following treatments:[18]

- External radiotherapy with chemotherapy and then more chemotherapy

- Chemotherapy followed by radiotherapy
- Chemotherapy on its own

Clinical Trial Information

Trial	**KEYNOTE-B21,** NCT04634877, 2020-003424-17; A Phase 3, Randomized, Double-Blind Study of Pembrolizumab Versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent **Phase III** – Recruiting **Locations:** 12 EU countries, UK, USA, Canada and other countries **Primary completion date:** June 2025
Trial Design	Randomised, parallel assignment, double-blinded
Population	N=990 (estimated); histologically confirmed new diagnosis of endometrial carcinoma or carcinosarcoma; has undergone curative intent surgery; is at high risk for recurrence following treatment with curative intent surgery; aged 18 and older
Intervention(s)	Pembrolizumab IV, carboplatin IV, paclitaxel IV, docetaxel IV, cisplatin IV, external beam radiotherapy, brachytherapy
Comparator(s)	Placebo for pembrolizumab IV, carboplatin IV, paclitaxel IV, docetaxel IV, cisplatin IV, external beam radiotherapy, brachytherapy
Outcome(s)	**Primary outcomes:** - Disease-free survival (DFS) as assessed radiographically by investigator or by histopathologic confirmation of suspected disease recurrence [Time frame: up to approximately 42 months] - Overall survival (OS) [Time frame: up to approximately 54 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate of solution for infusion vial costs £2,630.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Lenvatinib with pembrolizumab for untreated recurrent or advanced endometrial cancer (GID-TA10851). Expected date of issue to be confirmed.

- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015; updated: December 2021.
- NICE interventional procedures guidance. Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer (IPG256). September 2010.

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

- European Society of Gynaecological Oncology (ESGO). ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. 2021.[20]
- British Gynaecological Cancer Society. BGCS Uterine Cancer Guidelines: Recommendations for Practice. 2017.[21]
- European Society for Medical Oncology (ESMO). Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2013.[22]

Additional Information

References

1 Clinicaltrials.gov. *A Phase 3, Randomized, Double-Blind Study of Pembrolizumab Versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent (KEYNOTE-B21 / ENGOT-en11 / GOG-3053). Trial ID: NCT04634877*. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04634877 [Accessed 13 September 2022].

2 Electronic Medicines Compendium. *Keytruda 25 mg/mL concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/2498/smpc [Accessed 13 September 2022].

3 de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *The Lancet Oncology*. 2018;19(3):295-309. Available from: https://doi.org/10.1016/S1470-2045(18)30079-2.

4 Giudice E, Salutari V, Ricci C, Nero C, Carbone MV, Musacchio L, et al. Recent progress in the use of pharmacotherapy for endometrial cancer. *Expert Opinion on Pharmacotherapy*. 2022:1-12. Available from: https://doi.org/10.1080/14656566.2022.2106782.

5 European Society for Medical Oncology. *EMA Recommends Extension of Therapeutic Indications for Pembrolizumab.* 2022. Available from: https://www.esmo.org/oncology-news/ema-recommends-extension-of-therapeutic-indications-for-pembrolizumab [Accessed 13 September 2022].

6 National Institute for Health and Care Excellence. *Pembrolizumab.* Available from: https://bnf.nice.org.uk/drug/pembrolizumab.html [Accessed 13 September 2022].

7 Clinicaltrials.gov. *Search of: Pembrolizumab AND Merck Sharp & Dohme.* 2022. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Pembrolizumab+AND+Merck+Sharp+%26+Dohme&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&phase=1&phase=2 [Accessed 13 September 2022].

8 Cancer Research UK. *Types and grades of womb cancer.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/womb-cancer/types-grades [Accessed 21 September 2022].

9 Cancer Research UK. *Risks and causes of womb cancer.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/womb-cancer/risks-causes [Accessed 21 September 2022].

10 Cancer Research UK. *Symptoms of womb cancer.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/womb-cancer/symptoms [Accessed 21 September 2022].

11 Soble W, Tymon-Rosario J, Huang G. High-risk Endometrial Cancer: The Present and Future of Adjuvant Therapy. *Oncology & Haematology*. 2021;17:23. Available from: https://doi.org/10.17925/OHR.2021.17.1.23.

12 Cancer Research UK. *Uterine cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer [Accessed 21 September 2022].

13 Cancer Research UK. *Uterine cancer incidence statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence [Accessed 21 September 2022].

14 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21: Diagnosis.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 21 September 2022].

15 Office for National Statistics. *Cancer registration statistics, England.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 7 June 2022].

16 Office for National Statistics. *Cancer survival in England - adults diagnosed.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 9 June 2022].

17 National Health Service. *Womb (uterus) cancer: Treatment.* 2021. Available from: https://www.nhs.uk/conditions/womb-cancer/treatment/ [Accessed 21 September 2022].

18 Cancer Research UK. *Womb cancer treatment options.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/womb-cancer/treatment/decisions-about-treatment [Accessed 21 September 2022].

19 National Institute for Health and Care Excellence. *Pembrolizumab: solution for infusion.* Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 13 September 2022].

20 Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer*. 2021;31(1):12-39. Available from: https://doi.org/10.1136/ijgc-2020-002230.

21 Sundar S, Balega J, Crosbie E, Drake A, Edmondson R, Fotopoulou C, et al. BGCS uterine cancer guidelines: Recommendations for practice. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2017;213:71-97. Available from: https://doi.org/10.1016/j.ejogrb.2017.04.015.

22 Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2013;24:vi33-vi8. Available from: https://doi.org/10.1093/annonc/mdt353.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.