Health Technology Briefing
December 2023

Dostarlimab with paclitaxel and carboplatin for recurrent or primary advanced endometrial cancer

Company/Developer	GlaxoSmithKline UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 37641	NICE ID: Not available	UKPS ID: 672513

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Dostarlimab in combination with paclitaxel and carboplatin is in clinical development for the treatment of primary advanced or recurrent endometrial cancer. Endometrial cancer is cancer of the lining of the womb. Advanced cancer is when the cancer has spread to other parts of the body; recurrent cancer means the cancer has come back after treatment. Symptoms of endometrial cancer include abnormal bleeding from the vagina, pain during sex, lower back pain and blood in urine. Typically, advanced endometrial cancer is treated by using a combination of surgery, radiotherapy and/or chemotherapy. Prognosis of advanced/recurrent endometrial cancer is poor with limited treatment options. Therefore, there remains a need for additional targeted treatment options to improve outcomes for this patient population.

Dostarlimab is a type of protein known as a monoclonal antibody, that has been designed to block a receptor (target) called programmed cell death -1 (PD-1) on certain cells of the immune system. Some cancers can make proteins (PD-L1 and PD-L2) that combine with PD-1 to switch off the activity of the immune cells, preventing them from attacking the cancer. By blocking PD-1, dostarlimab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. If licensed, dostarlimab, administered via intravenous injection, in combination with chemotherapy will offer an additional treatment option for primary advanced and recurrent endometrial cancers.

Proposed Indication

Dostarlimab in combination with platinum-containing chemotherapy for the treatment of adult patients with recurrent or primary advanced endometrial cancer.[1]

Technology

Description

Dostarlimab (Jemperli) is a humanised monoclonal antibody of the IgG4-κ isotype that binds with high affinity to programmed cell death 1 (PD-1) receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway-mediated immune response results in inhibition of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti-tumour immune responses through blockade of PD-1 binding to PD-L1 and PD-L2, thereby increasing the immune system's ability to kill the cancer cells.[2,3]

Dostarlimab in combination with platinum-based chemotherapy is in clinical development for the treatment of recurrent or primary advanced endometrial cancer. In the phase III clinical trial (RUBY; NCT03981796) dostarlimab is administered intravenously at a dose of 500mg in combination with carboplatin and paclitaxel, every 3 weeks (six cycles), followed by dostarlimab (1000mg) or placebo every 6 weeks for up to 3 years.[4,5]

Key Innovation

Prognosis of advanced/recurrent endometrial cancer is poor, with a median survival of 12-15 months for patients with measurable disease. Treatment options are limited, with primary management being chemotherapy with carboplatin and paclitaxel.[6] Dostarlimab is an immune-checkpoint inhibitor that targets the PD-1 receptor. The combination of chemotherapy and immunotherapy may have synergistic effects in the treatment of endometrial cancer.[4]

If licensed, dostarlimab in combination with platinum-based chemotherapy will offer an additional treatment option for patients with primary advanced/recurrent endometrial cancer.

Regulatory & Development Status

Dostarlimab currently has Marketing Authorisation in the UK/EU in combination with platinum-based chemotherapy for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy.[2,3] It is also indicated as a monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.[3]

Dostarlimab is currently in phase II and III trials for the treatment of several indications, some of which include:[7]

- Non-small cell lung cancer
- Colorectal cancer
- Melanoma
- Endometrial cancer
- Liver cancer

Patient Group

Disease Area and Clinical Need

Endometrial cancer, also known as uterine or womb cancer, is the presence of cancer cells on the lining of the womb (endometrium).[8] Primary cancer is defined as the original site (organ or tissue) where cancer began.[9] Advanced endometrial cancer is defined as stage 3 or 4, where the cancer has spread into the surrounding tissues or organs and is less likely to be cured.[10,11] In stage 3, the spread of cancer is contained within the pelvis. Once the cancer has spread into another area of the body, it is classed as stage 4 or metastatic.[10] Recurrent endometrial cancer is when the cancer returns after primary treatment.[10] The cancer can recur anywhere, commonly in the abdominal cavity, lymph nodes, lung and vagina, which determines treatment.[10,12] 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), being overweight, having diabetes, treatment with tamoxifen, endometrial hyperplasia and factors relating to menstruation including starting early, late menopause and polycystic ovary syndrome.[13] Endometrial cancer has a devastating impact on life expectancy and quality of life.[14] Physical symptoms can be debilitating and include bleeding, pain, discomfort, reduced appetite, nausea and fatigue. Other symptoms can include swelling in the tummy or pelvis, pain in the pelvis or lower back, or during sex, or blood in the urine.[15]

Around 9,700 women are diagnosed with womb cancer in the UK each year. This makes it the 4th most common cancer in women in the UK.[8] Endometrioid carcinoma is the most common subtype, resulting in an estimated 2,162 deaths every year in the UK.[16] Recurrent or advanced endometrial cancer has a reported prognosis of 12 months or less and 5-year net survival rates of about 20%, compared with 89% for non-recurrent disease.[14] Almost three quarters of cases of endometrial cancer are in women aged 40 to 74; about 3% of endometrial cancers occur in women under 45 years of age.[10,13] In England (2022-23), there were 18,945 finished consultant episodes (FCE) and 17,713 admissions for endometrial cancer (ICD-10 code C54.1) which resulted in 29,419 FCE bed days and 9,996 day cases.[17]

Recommended Treatment Options

The initial treatment for endometrial cancer is usually to remove the womb (hysterectomy) and both the fallopian tubes and ovaries (bilateral salpingo-oophorectomy). In advanced endometrial cancer, debulking surgery may be carried out to remove as much of the cancer as possible. Radiotherapy may be used for people who cannot have surgery, or alongside surgical treatment. Chemotherapy can be used adjunct to surgery for people with stage 2-4 disease. Hormone therapy or chemotherapy may be used for cancer that has metastasised or relapsed.[10]

NICE currently recommends the following therapies for the treatment of advanced or recurrent endometrial cancer:

- Pembrolizumab with lenvatinib for patients with advanced or recurrent endometrial cancer that has progressed on or following prior treatment with a platinum containing regimen.[14]
- Dostarlimab for patients with mismatch repair deficient or microsatellite instability high (dMMR/MSI-H) advanced or recurrent endometrial cancer that has progressed on or following prior treatment with a platinum containing regimen.[18]
- 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.[19]

Clinical Trial Information

Trial	**RUBY**; NCT03981796, **EudraCT** 2019-001576-11; A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer (RUBY) **Phase III:** Active, not recruiting **Location(s):** 13 EU countries, UK, USA, Canada and other countries **Primary completion date:** November 2026
Trial Design	Randomised, quadruple masked, parallel assignment
Population	N=494 (part 1 of the RUBY trial only); patients aged 18 years or older with recurrent or primary advanced endometrial cancer with a low potential for cure by radiation therapy or surgery alone or in combination.
Intervention(s)	Dostarlimab + carboplatin-paclitaxel followed by dostarlimab.
Comparator(s)	Placebo + carboplatin-paclitaxel followed by placebo.
Outcome(s)	Primary outcome measures: • Part 1: Progression-Free Survival (PFS) - investigator assessment [time frame: up to 6 years] • Part 1: Overall survival [time frame: up to 6 years] See trial record for full list of other outcomes.
Results (efficacy)	Based on interim analysis one of RUBY Part 1 (data cut-off 28th Sep 2022)[a] in the overall population, PFS at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1% (95% CI, 13.0 to 23.9) in the placebo group (hazard ratio, 0.64; 95% CI, 0.51 to 0.80; P<0.001). Overall survival at 24 months was 71.3% (95% CI, 64.5 to 77.1) with dostarlimab and 55.1% (95% CI, 46.8 to 62.5) with placebo (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.87).[4,20]
Results (safety)	Based on interim analysis one of RUBY Part 1 (data cut-off 28th Sep 2022)[a] the most common adverse events that occurred or worsened during treatment were nausea (53.9% of the patients in the dostarlimab group and 45.9% of those in the placebo group), alopecia (53.5% and 50.0%), and fatigue (51.9% and 54.5%). Severe and serious adverse events were more frequent in the dostarlimab group than in the placebo group.[4]

Estimated Cost

The NHS indicative price of one dostarlimab concentrate for solution for infusion vial is £5,887.33 for 500mg/10ml.[21]

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.

[a] Information provided by GlaxoSmithKline UK Ltd

- NICE technology appraisal in development. Durvalumab for maintenance treatment of recurrent or advanced endometrial cancer (GID-TA11340). Expected date of issue to be confirmed.
- NICE technology appraisal in 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 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 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.

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 Guideline for diagnosis, treatment and follow-up. 2022.[22]
- British Gynaecological Cancer Society (BGCS). British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. 2021.[23]
- European Society of Gynaecological Oncology (ESGO). ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. 2021.[24]

Additional Information

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