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HEALTH TECHNOLOGY BRIEFING
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Dostarlimab in addition to carboplatin and paclitaxel for recurrent or primary advanced endometrial cancer

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Developer/Company	GlaxoSmithKline UK Ltd.	UKPS ID	655940

Licensing and market availability plans	Currently in phase III trials

SUMMARY

Dostarlimab in addition to carboplatin and paclitaxel is in development for recurrent or primary advanced endometrial cancer. Endometrial (uterine) cancer is cancer of the lining of the womb. Recurrent cancer is cancer that has come back after treatment. Advanced cancer is cancer that cannot normally be cured or controlled. Endometrial cancer is characterised by abnormal vaginal bleeding (after the menopause, between periods) and can also cause symptoms such as pain during sex and lower abdominal (tummy) pain. Typically, advanced endometrial cancer is treated by using a combination of surgery, radiotherapy and/or chemotherapy.

Dostarlimab is a type of immunotherapy (therapy that targets the immune system) that is administered intravenously (IV) and targets a receptor (protein) for PD-1. Blockage of PD-1 allows for the body's own immune cells (called T-cells) to attack and kill the cancer cells. If licensed, dostarlimab – in addition to carboplatin and paclitaxel – would offer an additional treatment option for patients with recurrent or primary advanced endometrial cancer.

PROPOSED INDICATION

Treatment of recurrent or primary advanced endometrial cancer.[1]

TECHNOLOGY

DESCRIPTION

Dostarlimab (Jemperli) is an investigational anti-programmed death (PD)-1 immunotherapy agent. Dostarlimab binds with high affinity to the PD-1 receptor, working to block its interaction with programmed death receptor ligands 1 and 2 (PD-L1 and PD-L2).[2] When PD-1 is bound to PD-L1, it helps keep T cells from killing other cells, including cancer cells. When dostarlimab blocks PD-L1 and PDL-2 binding to PD-1 the "brakes" on the immune system are released and the ability of T cells to kill cancer cells is increased.[3,4]

The phase III trial, RUBY (NCT03981796) is split into two parts. Part 1 is to evaluate the efficacy and safety of dostarlimab plus carboplatin-paclitaxel followed by dostarlimab monotherapy versus placebo plus carboplatin-paclitaxel followed by placebo.[1] In Part 1 patients will receive combination dostarlimab 500 mg or placebo + carboplatin AUC 5 + paclitaxel 175 mg/m2 every 3 weeks for 6 cycles followed by dostarlimab 1000 mg or placebo monotherapy every 6 weeks for up to 3 years in the absence of progressive disease, death, unacceptable toxicity, or patient/physician decision to withdraw from the study.[5]

INNOVATION AND/OR ADVANTAGES

In those women where surgery and/or radiotherapy is not curative, there is no approved UK treatment for recurrent or advanced newly diagnosed endometrial cancer. Women in this setting currently receive repeat carboplatin-paclitaxel as standard systemic anti-cancer therapy for recurrent or advanced endometrial cancer.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Dostarlimab (Jemperli) has a conditional European Medicines Agency (EMA) marketing authorisation as a monotherapy for the treatment of adult patients with recurrent or advanced dMMR/MSI-H endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.[4]

Dostarlimab is currently in phase II/III trials for the treatment of: ovarian cancer, head and neck cancer, melanoma, cervical cancer, pancreatic cancer and small-cell lung cancer, amongst others.[2,6]

PATIENT GROUP

DISEASE BACKGROUND

Endometrial cancer (uterine or womb cancer) is cancer of the lining of the womb.[7] The most common symptom is abnormal bleeding from the vagina (after the menopause, between periods or heavier periods). Less common symptoms include pain in the lower abdomen and pain during sex.[8]

The causes of uterine cancer are thought to be multifactorial, however, development of the disease is associated with exposure to oestrogen. Therefore, risk factors include the menopause, being overweight or obese, women who have not had children, previous history of taking tamoxifen (a breast cancer treatment), high levels of insulin, polycystic ovary syndrome (PCOS) and endometrial hyperplasia. Age is also a risk factor, with most cases occurring in women aged over 40.[9]

Recurrent cancer is cancer that has come back after a period of time during which the cancer could not be detected.[10] Advanced cancer is cancer that is unlikely to be cured or controlled with treatment.[11] Primary cancer refers to the first mass of cancer cells (tumour) in an organ or tissue. The tumour is confined to its original site, such as the endometrium lining.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, uterine cancer was the 4th most common cancer in the UK. There were approximately 9,500 new cases of uterine cancer in the UK in 2017. The age-standardised incidence rate in England for uterine cancer, in 2017, was 28.9 per 100,000 in females.[13]

Uterine cancer patients with a known stage are diagnosed at an early stage (81-83% are diagnosed at stage I or II); less are diagnosed at a late stage (18-19% are diagnosed at stage III or IV). Between 7% and 8% of uterine cancer patients have metastases at diagnosis (stage IV).[14] According to 2010-2012 data in the UK, most uterine cancer, 95-95% of cases, occur in the endometrium, with much smaller proportions in the myometrium, fundus uteri and isthmus uteri.[15]

In England in 2018-2019, there were 17,431 finished consultant episodes (FCE) and 16,262 hospital admissions for malignant neoplasm of endometrium (ICD 10: C54.1), resulting in 30,741 FCE bed days and 8,107 day cases.[16]

According to 2013-2017 data, 75.6% women diagnosed with uterine cancer in England survive their disease for five years or more.[17] Around 15 out of every 100 women (around 15%) will survive their cancer for 5 years or more after they are diagnosed with advanced uterine cancer.[17]

Uterine cancer is the 8th most common cause of cancer death in females in the UK in 2017. The age-standardised mortality rate in females in England was 7.2 per 100,000 in 2017.[18] Uterine cancer mortality is strongly related to age, with the highest mortality rates being in older women.[19] In the 2017 death registration in England and Wales, there were 2,101 deaths due to malignant neoplasm of other and unspecified parts of uterus (C54-C55) with the higher proportions in aged 65 and above.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

As per the 2017 BGCS guidelines, for patients with advanced disease, FIGO Stage III and IV disease at diagnosis, the primary treatment for endometrial cancer is surgery, which usually involves a total hysterectomy with bilateral salpingo-oophorectomy. For patients with advanced disease adjuvant and neo-adjuvant chemotherapy are also used in appropriate patients. The choice of chemotherapy will usually be carboplatin and paclitaxel.[21]

For patients with early stage disease, FIGO stage I and II at diagnosis, the primary treatment is surgery again, which usually involves a total hysterectomy with bilateral salpingo-oophorectomy. Patients with early stage disease who experience disease recurrence may receive chemotherapy similarly to patients with advanced disease, usually carboplatin and paclitaxel.[21]

CURRENT TREATMENT OPTIONS

The most common type of chemotherapy drugs for endometrial cancer are paclitaxel, carboplatin, cisplatin, doxorubicin, and cyclophosphamide. Patients may have a single drug or a combination of two or three drugs.[22]

No chemotherapy treatments are approved for recurrent or advanced first line endometrial cancer. Platinum-based chemotherapy is considered the standard of care with the most common regimen being carboplatin-paclitaxel.[23] In trial GOG0209, carboplatin-paclitaxel showed a median overall survival of 32 months and a median progression-free survival of 14 months in patients with 1L recurrent or advanced endometrial cancer.[24] While the combination of doxorubicin, cisplatin and paclitaxel have similar efficacy the regimen is not commonly used due to toxicity. [24,25]

PLACE OF TECHNOLOGY

If licensed, dostarlimab, in combination with carboplatin and paclitaxel, will offer an additional treatment option for recurrent or primary advanced endometrial cancer

CLINICAL TRIAL INFORMATION

Trial	**RUBY,** NCT03981796**,** 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 –** recruiting **Location:** EU (including UK), US and other countries **Primary completion date:** July 2021
Trial design	Randomised, parallel assignment, quadruple blinded
Population	Part 1: N = 470 (planned), adult females aged 18 years and older, endometrial cancer with recurrent or advanced disease
Intervention(s)	Dostarlimab 500mg IV Q3W for six, 21-day cycles then dostarlimab 1000mg every six weeks. Followed by carboplatin 5mg/mL/min and paclitaxel 175mg/m^2 IV from cycle one to cycle six[5]

Comparator(s)	Matched placebo carboplatin-paclitaxel followed by placebo[5]
Outcome(s)	Progression-free survival - based on blinded independent central review (BICR) [time frame: up to 6 years and 9 months] For full list of outcomes, see trial registry
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of dostarlimab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab for previously treated endometrial cancer (ID1205). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Lenvatinib with pembrolizumab for previously treated advanced, metastatic or recurrent endometrial cancer (ID3811). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (ID3802). Expected publication date: January 2022

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England 2013-2014. Standard Contract for Complex Gynaecology: Specialist Gynaecological cancers. E10/S/f
- 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.

OTHER GUIDANCE

- Sociedad Española de Oncologia Médica. SEOM clinical guidelines for endometrial cancer (2017). 2018.[26]
- British Gynaecological Cancer Society. BGCS uterine cancer guidelines: Recommendations for practice. 2017.[27]
- European Society for Medical Oncology. Endometrial cancer: ESMO clinical practice guidelines. 2013.[23]

ADDITIONAL INFORMATION

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