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HEALTH TECHNOLOGY BRIEFING
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Cemiplimab for recurrent, persistent or metastatic cervical cancer – second line

NIHRIO ID	20479	**NICE ID**	10120
Developer/Company	Sanofi	**UKPS ID**	650467

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

SUMMARY

Cemiplimab is in clinical development for the treatment of recurrent, persistent, or metastatic cervical cancer. Recurrent cancer is when the cancer returns months or years after the original treatment; persistent cancer is when the tumour does not respond to treatment or a second tumour develops despite the completion of treatment. Metastatic cancer is when the tumour has spread outside the original tumour site, to other areas of the body. If cervical cancer is recurrent, metastatic or persistent, there are limited treatment options, with treatments usually aiming to alleviate symptoms and improve quality of life.

Cemiplimab is a type of protein called an antibody, which can bind to PD-1 and prevent it interacting with PD-L1. Therefore, it allows the T-cells (a type of immune cell) to attack the cancer cells. Cemiplimab is administered by intravenous infusion (injection into the vein) once every three weeks. If licensed, cemiplimab would offer an additional treatment option for patients with recurrent, persistent or metastatic cervical cancer.

PROPOSED INDICATION

Second line treatment of female patients with recurrent, persistent and/or metastatic cervical cancer.[a]

TECHNOLOGY

DESCRIPTION

Cemiplimab (Libtayo, REGN2810) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands, programmed death ligand 1 and 2 (PD-L1 and PD-L2). Engagement of PD-1 with PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T cell function such as proliferation, cytokine secretion, and cytotoxic activity. Cemiplimab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[1] This may restore immune function through the activation of cytotoxic T-cells. PD-1, a transmembrane protein in the immunoglobulin superfamily expressed on activated T-cells, negatively regulates T-cell activation and effector function when activated by its ligand. As such, it plays an important role in tumour evasion from host immunity.[2]

Cemiplimab is currently in clinical development for the treatment of female patients with recurrent, persistent and/or metastatic cervical cancer. In the phase III clinical trial, NCT03257267, 350mg cemiplimab is administered as an IV infusion every 3 weeks.[3]

INNOVATION AND/OR ADVANTAGES

No pharmacological agent has been shown to improve overall survival (OS) after first-line chemotherapy for metastatic cervical cancer which results in a high mortality rate, therefore there is an unmet need for second-line treatment options.[4,5]

In a phase I clinical trial (NCT02383212) cemiplimab was found to induce response and provide clinical benefit for patients with recurrent or metastatic cervical cancer. This showed similar clinical benefit and safety profile to other PD-1 inhibitors.[4] Evidence from systematic reviews has demonstrated that PD-1 inhibitors may have a more beneficial effect for patients with metastatic or recurrent cancer result, and potentially lower adverse effects, in comparison to conventional therapies.[6,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Cemiplimab is licenced for specialist use only in adults with cutaneous squamous cell carcinoma.[8]

[a] Information provided by Sanofi on UK PharmaScan

Very common side-effects (affects >1/10 people) include rash/itching, tiredness, and diarrhoea. Common side-effects (affects up to 1/10 people) include thyroid gland problems, cough, lung inflammation, increased liver enzymes in the blood, joint pain, swelling, polyarthritis, joint effusion, abnormal kidney function, muscle or bone pain, shortness of breath, inflammation of the mouth, inflammation of the liver, and infusion-related reactions.[9]

Cemiplimab is in phase II clinical development for:[10]

- Metastatic pancreatic cancer
- Melanoma stages III-IV
- Unresectable melanoma
- Squamous cell carcinoma of the oropharynx
- Head and neck squamous cell carcinoma
- Hepatocellular carcinoma
- Invasive breast cancer
- Hepatitis B virus cervical cancer

It is also in phase III clinical development for:[10]

- Cutaneous squamous cell carcinoma
- Non-small cell lung cancer
- Squamous cell carcinoma

PATIENT GROUP

DISEASE BACKGROUND

The cervix is the lower part of the womb, also called the neck of the womb. The cervix is covered with a layer of skin-like cells on its outer surface, called ectocervix. Inside of the cervix, there are glandular cells that produce mucus called endocervix. The skin-like cells of the ectocervix can become cancerous, leading to squamous cell cervical cancer. This is the most common type of cervical cancer. The glandular cells of the endocervix can also become cancerous, leading to adenocarcinoma of the cervix.[11]

The main risk factors for cervical cancer include age, human papillomavirus (HPV) infection (HPV16 and HPV18), immune system deficiency, herpes, smoking status, socioeconomic factors, use of oral contraceptives and exposure to diethylstilbesterol (DES).[12]

The most common sign and symptoms of cervical cancer include blood spots or light bleeding between or following periods, menstrual bleeding that is longer and heavier than usual, bleeding (after intercourse, douching, or a pelvic examination), increased vaginal discharge, pain during sexual intercourse, bleeding after menopause, and unexplained, persistent pelvic and/or back pain.[13]

Recurrent cervical cancer occurs when the cancer is detected months or years after the completion of an initial cancer treatment regimen, which may have included surgery, radiation therapy and or chemotherapy. The recurrence of cervical cancer may be a local recurrence, which is contained in the cervix region. A metastatic recurrence occurs when cancer has

spread to other organs, such as the kidney, bladder, or lymph nodes. This recurrence happens when the cervical cancer cells break off from the original tumour and travel to other parts of the body through the lymphatic or circulatory system.[14] Persistent cancer is when a tumour has remained despite treatment, or when a second tumour has been diagnosed within three months after therapy was completed for an original tumour.[15]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK cervical cancer was the 14th most common cancer accounting for 2% of all new cancers cases in females in 2017.[16]

Between 2013-17 there were 12,849 women diagnosed with cervical cancer in England. The age-standardised 1-year and 5-year survival were 81.1% and 61.4% respectively.[17] European age-standardised incidence rates for cervical cancer are projected to rise by approximately 43% in the UK between 2014 and 2035.[18]

In England (2019-20) there were 9,451 finished consultant episodes (FCE) of patients with a main diagnosis of malignant neoplasm of cervix uteri (ICD-10 code C53). Of these FCE there were 5,613 day cases and 14,491 bed days.[19] In England and Wales in 2017, there were 730 deaths with C53 recorded as the underlying cause.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of cervical cancer depends on several factors including the type and stage of cancer, possible side effects and patient's preference and overall health. Depending on the stage of cervical cancer treatment options may include surgery, chemotherapy and radiotherapy together (chemoradiotherapy), radiotherapy, and chemotherapy.[21]

Advanced cervical cancer (stage 2B, 3 and 4A) is usually treated with chemoradiotherapy while for cervical cancer that has spread further away in the body such as to the lungs (stage 4B or metastatic cancer), chemotherapy, radiotherapy and other medicines to help with symptoms are used as treatment options.[21]

Surgery is also sometimes used for people with advanced cervical cancer. In patients with recurrent cancer, pelvic exenteration (removal of the cervix, vagina, womb, ovaries, bladder and rectum) is offered.[21] Surgical resection or radiotherapy may potentially be curative for selected women with locally recurrent or metastatic disease, however in the majority of cases this will not be feasible. Women with recurrent and metastatic cervical cancer have limited systemic treatment options.[22]

CURRENT TREATMENT OPTIONS

According to the current National Institute for Health and Care Excellence (NICE) treatment pathway for women with recurrent and stage 4B cervical cancer, topotecan with cisplatin is recommended as a treatment option only if they have not previously received cisplatin. Women who have previously received cisplatin and are currently being treated with topotecan in combination with cisplatin, for recurrent and stage 4B cervical cancer, should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.[23]

PLACE OF TECHNOLOGY

If licensed, cemiplimab will offer a second line treatment option for adult patients with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy.

CLINICAL TRIAL INFORMATION

Trial	**NCT03257267; 2017-000350-19; An Open-Label, Randomized, Phase 3 Clinical Trial of REGN2810 Versus Investigator's Choice of Chemotherapy in Recurrent or Metastatic Cervical Carcinoma** **Phase III –** Active, not recruiting **Location(s):** Europe (incl UK), US, Canada, and others **Primary completion date:** May 2021
Trial design	Open-label, randomised, parallel assignment
Population	N=590 (estimated); adult females aged 18 years and older; recurrent, persistent and/or metastatic cervical cancer with squamous cell histology
Intervention(s)	350mg cemiplimab by intravenous (IV) administration every 3 weeks
Comparator(s)	Best standard of care (pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine)
Outcome(s)	Overall survival (OS) [Time frame: time from randomisation up to approximately 44 months]. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Libtayo 350mg/7ml concentrate for solution for infusion (active ingredient: cemiplimab 50mg/1ml) 1 vial (POM) has a NHS indicative price of £4,650.00 (hospital only).[24]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. LN-145 for treating recurrent, persistent or metastatic cervical cancer (TA10728). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer (TA10669). Expected date of issue to be confirmed
- NICE technology appraisal guidance in development. Tisotumab vedotin for treating recurrent or metastatic cervical cancer after systemic therapy (TA10620). Expected date of issue to be confirmed
- NICE technology appraisal guidance. Topotecan for the treatment of recurrent and stage IVB cervical cancer (TA183). October 2009

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: Chemotherapy (Children, teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- British Gynaecological Cancer Society. Cervical cancer guidelines: Recommendations for practice. September 2020[25]
- NHS Clinical Knowledge Summary. Cervical cancer and HPV. September 2020[26]
- European Society Medical Oncology. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. July 2017[27]
- World Health Organisation. Comprehensive cervical cancer control, a guide to essential practice (Second edition). December 2014[28]

ADDITIONAL INFORMATION

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