# Health Technology Briefing
# May 2022

# Pembrolizumab with chemoradiotherapy for treating high-risk locally advanced cervical cancer

| Company/Developer | Merck Sharp & Dohme Ltd. |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 29563 | NICE ID: 10690 | UKPS ID: 661665 |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials.

## Summary

Pembrolizumab in combination with chemoradiotherapy is in clinical development for the treatment of patients with high-risk, locally advanced cervical cancer. Cervical cancer arises when abnormal cells lining the cervix begin to grow uncontrollably and create tumours. Cervical cancer may not present symptoms, however the most common symptoms seen are unusual vaginal bleeding, pain during sex, vaginal discharge and pain in the pelvis. Increasing age and human papilloma virus (HPV) infection are risk factors for the development of cervical cancer. Locally advanced cervical cancer means there is a large tumour in the cervix and/or it has grown into the tissues around the cervix, but it has not spread to other organs. Treatment with a combination of radiation therapy and chemotherapy (chemoradiotherapy) is currently recommended for previously untreated, locally advanced cervical cancer patients.

Pembrolizumab is an intravenously (IV) administered 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, 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. High-risk locally advanced cervical cancer has a poor prognosis and the activity of pembrolizumab may be enhanced by combining it with chemoradiotherapy. If licensed, pembrolizumab in combination with chemoradiotherapy will offer an additional treatment option for patients with high-risk, locally advanced cervical cancer.

## Proposed Indication

First-line treatment of high-risk, locally advanced, FIGO 2014 stage IB2-IIB (with node-positive disease) or FIGO 2014 stages III-IVA cervical cancer.[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 chemoradiotherapy is currently in phase III clinical development for the first line treatment of high risk, locally advanced, FIGO 2014 stage IB2-IIB (with node-positive disease) or FIGO 2014 stages III-IVA cervical cancer. In the phase III trial, KEYNOTE-A18 (NCT04221945), pembrolizumab 200mg will be administered every three weeks (Q3W) via intravenous infusion (IV) for 5 cycles, followed by pembrolizumab 400mg IV every six weeks (Q6W) for an additional 15 cycles. During the Q3W dosing period of pembrolizumab, participants receive concurrent standard of care chemoradiotherapy. This includes cisplatin 40mg/m$^2$ IV once per week (QW) plus external beam radiotherapy (EBRT) followed by brachytherapy.[1]

### Key Innovation

High-risk locally advanced cervical cancer has a poor prognosis, and this cancer recurs within 2 years for over 50% of patients. EBRT with concurrent chemotherapy followed by brachytherapy is the standard of care for locally advanced cervical cancer. The immunostimulatory activity of the PD-1 inhibitor pembrolizumab may be enhanced by concurrent chemoradiotherapy.[3] If licensed, pembrolizumab in combination with chemoradiotherapy will offer an additional treatment option for patients with locally advanced cervical 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:[2,4,5]

- 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

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:[6]

- Hepatocellular carcinoma (HCC)

- Bladder cancer
- Ovarian cancer
- Prostate cancer

## Patient Group

### Disease Area and Clinical Need

Cervical cancer occurs when abnormal cells in the lining of the cervix grow in an uncontrolled way and eventually form a tumour.[7] Cervical cancers can be split in to two main forms, according to the type of cell that has become cancerous: squamous cell carcinomas (the most common form) and adenocarcinomas.[8] High risk patients are defined as lymph node positive, parametrial involvement and positive margins, and they gain a survival benefit from receiving post-operative cisplatin-based chemo-radiation.[9] Locally advanced cervical cancer is anything from stage 1B2 to stage 4A and it is defined as there being a large tumour within the cervix (more than 2cm in greatest dimension) and/or it has grown into the tissues beyond the cervix.[10,11] Human papilloma virus (HPV) infection is a major cause of the main types of cervical cancer, but other risk factors include age, smoking, long term oral contraceptive use and family history of cervical cancer.[12] Cervical cancer often has no obvious symptoms and may not cause any symptoms until it has reached an advanced stage. The most common symptoms which may present include unusual vaginal bleeding, pain or discomfort during sex, vaginal discharge and pelvic pain.[13]

Cervical cancer is the 14th most common cancer in females in the UK, accounting for 2% of all new cancer cases in females (2016-18).[14] The age standardised incidence rate of cervical cancer for females in England is 9.5 per 100,000.[15] In England (2020-21), there were 8,091 finished consultant episodes (FCEs) and 7,586 admissions for malignant neoplasm of cervix uteri (ICD-10 code C53), which resulted in 4,719 day cases and 11,296 FCE bed days.[16]

In England (2017), there were 2,591 patients diagnosed with malignant neoplasm of cervix uteri and 674 deaths registered where malignant neoplasm of cervix uteri was the underlying cause.[17] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for cervical cancer were 81.1% and 61.4% respectively.[18]

### Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends chemoradiation as first-line therapy for the treatment of locally advanced cervical cancer. This involves treatment with EBRT, intracavity brachytherapy and concomitant chemotherapy.[19]

## Clinical Trial Information

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| Trial | **KEYNOTE-A18, NCT04221945, 2019-003152-37;** A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer<br>**Phase III** – Recruiting<br>**Locations:** 11 EU countries, UK, USA, Canada and other countries<br>**Primary completion date:** February 2024 |
| Trial Design | Randomised, parallel assignment, triple-masked |
| Population | N=980; aged 18 years and older; subjects with high-risk locally advanced cervical cancer; has histologically-confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix; has ECOG PS 0- |

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| | 1, radiographically evaluable disease per RECIST 1.1 and adequate organ function; has not previously received any definitive surgical, radiation, or systemic therapy for cervical cancer, including investigational agents, and is immunotherapy-naïve |
| Intervention(s) | Pembrolizumab IV, cisplatin IV, EBRT and brachytherapy |
| Comparator(s) | Placebo for pembrolizumab IV, cisplatin IV, EBRT and brachytherapy |
| Outcome(s) | Primary outcomes:<br>• Progression-free Survival (PFS) per response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) as assessed by the investigator [Time frame: up to approximately 38 months]<br>• Overall Survival (OS) [Time frame: up to approximately 46 months]<br><br>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.[20]

Cisplatin is already marketed in the UK; a 100mg/100ml concentrate of solution for infusion vial costs between £50.22 and £55.64.[21]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal awaiting development. Durvalumab with chemoradiation for untreated locally advanced cervical cancer (GID-TA10963). Expected date of issue to be confirmed.
- NICE interventional procedures guidance. High dose rate brachytherapy for carcinoma of the cervix (IPG160). March 2006.

### 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). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

### Other Guidance

- British Gynaecological Cancer Society. British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: Recommendations for practice. 2020.[9]
- ESMO. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[22]

## Additional Information

## References


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***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.***