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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in addition to chemotherapy for persistent, recurrent or metastatic cervical cancer – first line

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Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	654817

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

SUMMARY

Pembrolizumab, in addition to chemotherapy, is being developed for the treatment of persistent, recurrent or metastatic cervical cancer. Cervical cancer develops in the lower part of the womb and mainly affects sexually active women aged between 30 and 45 years. Cervical cancer that has spread to another part of the body is called advanced or metastatic cancer. Cancer that returns after months or years of the completion of the initial treatment is called recurrent cancer. Whilst chemoradiotherapy (chemotherapy and radiotherapy) is offered to patients with cervical cancer, women with recurrent or metastatic cervical cancer represent a poor prognostic group with high, unmet clinical needs.

Pembrolizumab is an immunomodulatory medicinal product, meaning that it helps the immune system to recognise and attack cancer cells. It is administered by intravenous infusion and is currently licensed in the UK for melanoma, non-small cell lung cancer and urothelial cancer – amongst others. If licensed, pembrolizumab, in addition to chemotherapy, would offer an alternative treatment for those with advanced, recurrent or metastatic cervical cancer.

PROPOSED INDICATION

First line treatment of persistent, recurrent, or metastatic cervical cancer.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against the human cell surface receptor PD-1 (programmed cell death-1) with potential immune checkpoint inhibitory and anti-neoplastic (anti-tumour) activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signalling receptor expressed on the surface of activated T-cells, and blocks the binding to and activation of PD-1 by its natural ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. Natural ligand activated PD-1 negatively regulates T-cell activation and plays a key role in in tumour evasion from host immunity. These natural ligands for PD-1 include programmed cell death ligand 1 (PD-L1), which is overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen presenting cells such as macrophages (white blood cells).[2]

Pembrolizumab being tested in a phase III clinical trial for use in combination with chemotherapy for the first-line treatment of persistent, recurrent or metastatic cervical cancer (NCT03635567, KEYNOTE-826). On day one of a 21 day cycle (for up to 35 cycles) patients in the trial will receive an intravenous infusion of 200mg pembrolizumab in combination with the investigator choice of chemotherapy - either 175mg/m^2 paclitaxel plus 50mg/m^2 cisplatin with/without 15mg/Kg bevacizumab OR 175mg/m^2 paclitaxel plus 5 AUC (area under the curve) carboplatin with/without 15mg/Kg bevacizumab. All treatments are administered until disease progression or toxicity for a maximum of ~ 2 years.[1]

INNOVATION AND/OR ADVANTAGES

Approximately 70% of cervical cancers express PD-L1; the majority of these PD-L1 positive cancers are squamous cell carcinomas, although PD-L1 expression is also observed in adenocarcinomas.[3]

Pembrolizumab binds PD-1 and therefore inhibits the binding of PD-L1 to its receptor. In the clinical trial, KEYNOTE-158, there was a 14.3% objective response to pembrolizumab,[3] therefore the US FDA granted accelerated approval for pembrolizumab for PD-L1–positive cervical cancer for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS) ≥1.[4]

Currently, patients with advanced cervical carcinoma are offered chemoradiation (radiation therapy plus chemotherapies such as cisplatin, carboplatin, paclitaxel, topotecan).[5] Bevacizumab in combination with paclitaxel and cisplatin/carboplatin may also be offered by some cancer alliances.[6] Topotecan in combination with cisplatin, is recommended as a treatment option for women with recurrent or stage IVb cervical cancer - if they have not previously received cisplatin.[7] However, women with recurrent or metastatic cervical cancer represent a poor prognostic group with high, unmet clinical needs.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced in the UK both as a monotherapy and in combination with other therapeutic agents for the following indications:[8]

- As a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults
- As a monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- As a monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
- In combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive tumour mutations
- In combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults
- As a monotherapy for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYRUDA
- As a monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- As a monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- As a monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10
- As a monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of metastatic or unrescetable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥1
- As a monotherapy for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥50% TPS and progressing on or after platinum-containing chemotherapy
- In combination with axitinib for the first-line treatment of advanced renal cell carcinoma in adults

In combination with chemotherapy, pembrolizumab can cause adverse effects such as anaemia, neutropenia, thrombocytopaenia, hypokalaemia, decreased appetite, dizziness, headache, peripheral neuropathy, dysgeusia, nausea, vomiting, diarrhoea, constipation, abdominal pain, rash, alopecia, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, pyrexia, oedema, increased blood creatinine.[8]

PATIENT GROUP

DISEASE BACKGROUND

Cervical cancer is the abnormal growth of cells in the lining of the cervix (the lower part of the womb). The cancer can occur in the endocervix (skin-like cells on the outer surface) leading to adenocarcinoma or in the ectocervix (mucosal cells) leading to squamous cell cervical cancer – the most common type of cervical cancer.[9]

The early stages of cervical cancer are symptomless, therefore screening is encouraged in women over 25 years, in order to detect cancer in the early stages. In later stage cancers, symptoms include unusual vaginal bleeding (after sex, between periods or after the

menopause), dyspareunia (pain or discomfort during sex), vaginal discharge and/or pelvic pain.[10]

The greatest risk factor for cervical cancer is being positive for the human papilloma virus (HPV), with 70% of cervical cancers being caused by HPV16 and HPV18. Women are also at higher risk of developing cervical cancer if they are positive for human immunodeficiency virus (HIV) or other sexually transmitted diseases such as chlamydia; if they are on a prescription of the contraceptive pill; if they have had children at a young age (<25 years old); if they have a family history of the disease or have had previous cancers such as cancer of the vagina, vulva kidney or urinary tract.[11]

When diagnosed, cervical cancer is staged from I to IV:[12]

- Stage I – cancer is contained within the neck of the womb (cervix)
- Stage II – the cancer has spread outside of the cervix into the surrounding tissue
- Stage III – the cancer has spread outside the cervix into the structures around it
- Stage IV – the cancer has spread to the bladder, rectum or further away

Locally advanced cervical cancer encompasses stage Ib2, to IVa cancer, which means that the cancer has spread to tissues surrounding the cervix. Advanced metastatic cancer is when the cancer has spread outside of the cervix to regions of the body away from the cervix such as the lungs. 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, or a metastatic recurrence, which 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.[12,13]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK in 2017, cervical cancer was the 14th most common cancer accounting for 2% of all new cancers cases in females.[14] In England in 2017, there were 2,591 registrations of newly diagnosed cases of malignant neoplasm of cervix uteri (ICD-10 code C53) and the direct age standardised rate per 100,000 population was 9.4.[15] European age-standardised incidence rates for cervical cancer are projected to rise by approximately 43% in the UK between 2014 and 2035, from 12 to 17 cases per 100,000 by 2035.[16]

In England, in 2018-19 there were 9,321 finished consultant episodes (FCEs) for malignant neoplasm of cervix uteri (ICD-10 code C53) and 8,702 admissions resulting in 14,033 bed days and 5,656 day cases.[17]

In England and Wales in 2017, there were 730 deaths with malignant neoplasm of cervix uteri (ICD-10 code C53) recorded as the underlying cause.[18] The age-standardised 1-year and 5-year survival for females diagnosed with cervical cancer in England in 2017 was 81.1% and 61.4% respectively.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of cervical cancer is based on several factors including the type and stage of the cancer, as well as the possible side effects of the treatment. In addition, in advanced cancer, patients may opt for treatments that reduce symptoms.[19-21]

Depending on the stage of cervical cancer treatment options may include surgery, chemotherapy and radiotherapy together (chemoradiotherapy), radiotherapy, and chemotherapy.[19]

Advanced cervical cancer is treated with chemotherapy, with or without radiotherapy. Surgery is also sometimes used. In patients with recurrent cancer, pelvic exenteration (removal of the cervix, vagina, womb, ovaries, bladder and rectum) is offered.[19]

Surgical resection or radiotherapy may potentially be curative for selected women with locally recurrent disease, however, in the majority of cases this will not be feasible. Thus, women with recurrent and metastatic cervical cancer have limited systemic treatment options.[22]

CURRENT TREATMENT OPTIONS

In the UK, chemotherapy is offered to patients with advanced, metastatic or recurrent cervical cancers. These include:[23]

- Cisplatin
- Carboplatin
- Paclitaxel (Taxol)
- Paclitaxel-carboplatin
- Topotecan (Hycamtin, postactasol)
- Carboplatin-etoposide

NICE recommends topotecan in combination with cisplatin for women with recurrent or stage IVb cervical cancer if they have not previously received cisplatin.[24] The British Gynaecological Cancer Society recommends that those patients who are WHO performance status (WHO PS) 0/1 should be considered for systemic treatment whereas for those with lower performance status should be carefully risk assessed. Since 2014 bevacizumab has been FDA approved and SMC and NICE approved from 2016 to be used with either platinum/paclitaxel or platinum/topotecan. [25]

P LACE OF TECHNOLOGY

If licensed, pembrolizumab, in addition to chemotherapy, will offer an additional treatment option for patients with persistent, recurrent or metastatic cervical cancer.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**MK-3475-826/KEYNOTE-826**; NC03635567; **EudaractCT** 2018-001440-53; A Phase 3 Randomised, Double-blind, Placebo-controlled trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent or Metastatic Cervical Cancer; Phase III Location: Europe (excluding the UK), US, Canada and other countries
Trial design	Randomised, double-blind, placebo-controlled
Population	N=600 (planned), females aged 18 years and older, persistent, recurrent or metastatic squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix

	which has not been treated with systemic chemotherapy and is not amenable to curative treatment.
Intervention(s)	Intravenous infusion of 200mg pembrolizumab in combination with the investigator choice of chemotherapy
Comparator(s)	Intravenous infusion of placebo in combination with the investigator choice of chemotherapy
Outcome(s)	• Progression free survival per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) as assessed by Blinded Independent Central Review (BICR) [Time frame: up to approximately 2 years] • Overall survival [Time frame: up to approximately 2 years] See clinical trial for full list of outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 50mg vial costs £1315.00/a pack; a 25mg/mL solution costs £2630.00/vial. Treatment with 200mg on day 1 of a 21 day cycle would cost £184,100 for 35 cycles.[26]

RELEVANT GUIDANCE

NICE GUIDANCE

- National Cancer Drugs Fund List. Bevacizumab for the first line treatment of recurrent or metastatic cervical cancer in combination with chemotherapy. (BEV2_v1.4) April 2020.
- 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

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ADDITIONAL INFORMATION

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