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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in addition to platinum therapy and radiation for unresectable locally advanced head and neck squamous cell carcinoma

NIHRIO ID	24115	**NICE ID**	10210
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	651425

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

SUMMARY

Pembrolizumab in addition to platinum therapy and radiation is in clinical development for the treatment of unresectable locally advanced head and neck squamous cell carcinoma. Cancers that are collectively known as head and neck cancers usually begin in the squamous cells that line the moist, mucosal surfaces inside the head and neck (for example, inside the mouth, the nose, and the throat). The main risk factors for squamous cell carcinomas are smoking tobacco and drinking alcohol. Symptoms may include sore throat, difficulty swallowing and pain in the ears and others. Treatment options for cancer that has spread usually involve chemotherapy such as (platinum-based therapy) and/or radiotherapy and focus on relieving symptoms and prolonging life rather than curing the cancer.

Pembrolizumab, given by intravenous infusion, is a monoclonal antibody that acts by binding to and blocking a protein called programmed death-ligand 1 (PD-L1) that is found on the cancer cells or immune cells trying to attack cancer cells. Binding to this protein can lead to the activation of the body's immune system to fight tumour cells. If licensed pembrolizumab in addition to platinum therapy and radiation will be a treatment option for patients with unresectable locally advanced head and neck squamous cell carcinoma.

PROPOSED INDICATION

Pembrolizumab in addition to platinum therapy and radiation for the treatment of patients with unresectable locally advanced head and neck squamous cell carcinoma[a]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody (mAb) 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.[1]

Pembrolizumab in addition to platinum therapy (cisplatin) and radiation is in clinical development for the treatment of unresectable locally advanced head and neck squamous cell carcinoma. In the phase III clinical trial (NCT03040999, MK-3475-412/KEYNOTE-412), both pembrolizumab and cisplatin (100mg/m^2) are administered as an intravenous (IV) infusion every 3 weeks. Participants will receive a priming dose of pembrolizumab before initiation of chemoradiation (CRT) (either accelerated or standard fractionation radiotherapy regimen).

During CRT, participants will receive 2 doses of pembrolizumab and up to 3 cycles of Cisplatin (2 cycles during accelerated and 3 cycles during standard fractionation radiotherapy). Participants will also receive up to an additional 14 cycles of pembrolizumab alone as maintenance therapy for a total of 17 cycles of pembrolizumab. If cisplatin and/or radiation therapy is discontinued, the participant may continue on treatment with pembrolizumab.

The radiotherapy is administered in 35 fractions (using 70 gray) over 6 and 7 weeks for the accelerated and standard radiotherapy respectively.[2]

INNOVATION AND/OR ADVANTAGES

Pembrolizumab as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic Head and Neck Squamous Cell Carcinoma (HNSCC),.[1] Cisplatin is indicated for the treatment of advanced or metastasised head and neck squamous cell carcinoma.[3] The combination of pembrolizumab with chemoradiation is not currently licensed for any indication.

Preclinical data suggest improved tumour growth control and survival when radiation therapy is combined with a PD-1 inhibitor. Pembrolizumab is effective for treatment of recurrent/metastatic HNSCC, and initial results from a phase 1b study suggest that pembrolizumab plus chemoradiation therapy is tolerable in patients with locally advanced (LA) HNSCC.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:[1]

- advanced (unresectable or metastatic) melanoma in adults

[a] Information provided by MSD on UKPharmaScan

- as an adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection
- metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations – first line
- locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen
- adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- 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 ≥ 10
- recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy

Pembrolizumab in combination with pemetrexed and platinum chemotherapy is licensed in the UK for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.[1]

The most common adverse events of pembrolizumab (affecting more than one in ten people) include anaemia, neutropenia, thrombocytopenia, decreased appetite, diarrhoea, nausea, vomiting, constipation, rash, pruritus and fatigue, asthenia, oedema, dysgeusia, and increased alanine aminotransferase.[1]

Pembrolizumab is currently in phase II and III clinical trials for the treatment of multiple malignant conditions such as breast cancer, colorectal cancer, prostate cancer etc.[5]

PATIENT GROUP

DISEASE BACKGROUND

Head and neck squamous cell carcinoma (HNSCC) is a cancer that arises from particular cells called squamous cells. Squamous cells are found in the outer layer of skin and in the mucous membranes, which are the moist tissues that line body cavities such as the airways and intestines. HNSCC develops in the mucous membranes of the mouth, nose and throat.[6]

Head and neck cancer refers to a group of biologically diverse cancers that start in the upper aerodigestive tract (UAT), including:

- Oral Cancer (mouth, lip and oral cavity)
- Cancer of the larynx (voice box)
- Cancer of the pharynx (throat)
- Thyroid cancer (please see below)
- Other head & neck cancers

The majority of non-thyroid head and neck cancers are squamous cell carcinomas. Head and neck cancers often spread to the lymph nodes of the neck, and this is often the first sign of the disease at the time of diagnosis.[7]

HNSCC is caused by a variety of factors that can alter the DNA in cells. The strongest risk factors for developing this form of cancer are tobacco use (including smoking or using chewing tobacco) and heavy alcohol consumption. In addition, studies have shown that infection with certain strains of human papillomavirus (HPV) is linked to the development of HNSCC. HPV infection accounts for the increasing incidence of HNSCC in younger people.[6] However, in developed countries, more than half of new HNSCC cases are diagnosed in people aged 65 years or older.[8] Researchers have identified mutations in many genes in people with HNSCC, however, it is not yet clear what role most of these mutations play in the development or progression of cancer. The proteins produced from several of the genes associated with HNSCC, including TP53, NOTCH1, and CDKN2A, function as tumour suppressors, which means they normally keep cells from growing and dividing too rapidly or in an uncontrolled way. When tumour suppressors are impaired, cells can grow and divide without control, leading to tumour formation. It is likely that a series of changes in multiple genes are involved in the development and progression of HNSCC.[6]

The symptoms of head and neck cancers may include a lump or a sore that does not heal, a sore throat that does not go away, difficulty or pain in swallowing and a change or hoarseness in the voice. Other symptoms that may affect specific areas of the head and neck include bleeding of the mouth, swelling of the jaw, ear pain, headaches, paralysis of the muscles in the face, etc.[9]

In addition to the life threatening nature of HNSCC, quality of life may also be affected as the head and the neck are anatomical sites of basic functions, including speech, swallowing, hearing and breathing, which are necessary for social interaction.[10]

CLINICAL NEED AND BURDEN OF DISEASE

Head and neck cancer is the 8th most common cancer in the UK, accounting for 3% of all new cancer cases in 2015. About 70% of head and neck cancer cases in the UK are in males.[11] The most common type of head and neck cancer is squamous cell carcinoma (approximately 90%).[12]

The annual incidence of head and neck cancer in England is estimated to be 0.024% and 0.010% for males and females (2014 data), respectively, equating to approximately 9,000 new diagnoses each year. Approximately 60% of patients present with locally advanced disease at diagnosis. In most of these patients, the disease reoccurs, with approximately 20–30% developing distant metastases. Survival depends on several factors, mainly the origin of the cancer and the stage of the disease at diagnosis.[12]

The age-standardised incidence rate of HNSCC in England was 19.2 per 100,000 population 2015, accounting for 3% of total cancer cases during the same year.[13] In 2017-18, there were 356 hospital admissions, and 386 finished consultant episode bed days due to malignant neoplasm of other and ill-defined sites: head, face and neck (C76.0) in England.[14]

The age-standardised five-year survival rates for head and neck cancers in adults aged 15-90 years in England (2009 – 2013) were as follows: 27.8% for hypopharyngeal cancer, 65.4% (men only) for laryngeal cancer, 56.1% for oral cavity cancer, 65.6% for oropharyngeal cancer, 67% for salivary glands cancer, 51.4% for sinus cancer and 60.3% for tongue cancer.[15]

Head and neck cancer is the 16th most common cause of cancer death in the UK, accounting for 2% of all cancer deaths (2016). There are around 3,900 head and neck cancer deaths in the UK every year (2014-16).[16] The disease control rate for locally advanced HNSCC is about 40% at 5 years.[17]

Locally advanced (stage III and IVA, IVB) head and neck squamous cell carcinoma accounts for around 60–70% of all presentations.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Head and neck tumours can occur at a large number of sub-sites, often invading more than one site.[12] Each has its own particular problems regarding management. Patients are often in poor general health and may have appreciable comorbidities or psychosocial problems.

Different members of the multidisciplinary team need to collaborate to devise the best management plan for each patient. Treatment options for HNSCC vary according to the specific site of the primary tumour. Smoking and alcohol cessation interventions can help in treatment and improve overall outcome, but may not have an effect on established tumours. Inoperable disease may be treated with combinations of chemotherapy and radiotherapy, but outcomes generally remain poor, and in some cases of advanced disease only patients' symptoms can be treated.[19]

Platinum-based chemotherapy is commonly used for recurrent or metastatic head and neck cancer.[12]

CURRENT TREATMENT OPTIONS

The standard treatment is concurrent chemotherapy and radiotherapy. For patients with poor prognosis, the recommended treatment is radiotherapy with or without concurrent chemotherapy. Treatments are traditionally delivered at daily fractions of 1.8 to 2 Gray, to approximately 70 Gray over 6 to 7 weeks, with local control rates of 50% to 70% for locoregionally advanced disease.[20,21]

Inhibition of the epidermal growth factor receptor (EGFR) with the monoclonal antibody cetuximab has been shown to lead to improvements in disease-free and overall survival when combined with radiotherapy in stage III/IV disease.[20]

PLACE OF TECHNOLOGY

If licensed, Pembrolizumab in addition to platinum therapy and radiation will be a treatment option for patients with unresectable locally advanced head and neck squamous cell carcinoma.

CLINICAL TRIAL INFORMATION

Trial	**MK-3475-412/KEYNOTE-412,** NCT03040999, EudraCT-2016-003934-25**; adult aged 18 years and older; Pembrolizumab vs placebo both in combination with chemoradiation; Phase III**
Sponsor	Merck Sharp and Dohme Corp.
Status	Ongoing
Source of Information	Trial registry[2]
Location	10 EU countries (incl UK), Canada, USA and other countries
Design	Randomised/controlled/parallel assignment.
Participants	N=780 (planned); aged 18 years and older; new diagnosis of oropharyngeal p16 positive, oropharyngeal p16 negative, or larynx/hypopharynx/oral cavity

	(independent of p16) squamous cell carcinoma; evaluable tumour burden; eligible for definitive chemoradiation (CRT) and not considered for primary surgery
Schedule	Participants are randomised to: • Pembrolizumab + Cisplatin + CRT Participants receive a priming dose of pembrolizumab before initiation of CRT (either accelerated or standard fractionation radiotherapy regimen). During CRT, participants receive 2 doses of pembrolizumab and up to 3 cycles of Cisplatin (2 cycles during accelerated and 3 cycles during standard fractionation radiotherapy). Participants also receive up to an additional 14 cycles of pembrolizumab alone as maintenance therapy for a total of 17 cycles of pembrolizumab. If cisplatin and/or radiation therapy is discontinued, the participant may continue on treatment with pembrolizumab. • Placebo + Cisplatin + CRT Participants receive placebo before initiation of CRT (either accelerated or standard fractionation radiotherapy regimen). During CRT, participants receive 2 doses of placebo and up to 3 cycles of Cisplatin (2 cycles during accelerated and 3 cycles during standard fractionation radiotherapy). Participants also receive up to an additional 14 cycles of placebo alone for a total of 17 cycles of placebo. If cisplatin and/or radiation therapy is discontinued, the participant may continue on treatment with placebo.
Follow-up	Up to five years
Primary Outcomes	Event-free survival (EFS) (Time frame: up to 5 years)
Secondary Outcomes	• Overall survival (Time frame: up to 5 years) • Adverse events (AEs) (Time frame: From time of first dose of study treatment until the end of follow up to 5 years) • Treatment discontinuations due to AEs (Time frame: From time of first dose of study treatment until the end of follow up to 1 year) • Global health status/quality of life (GHS/QoL) (Time frame: prior to first dose of study treatment and at the time of last follow up to 5 years) • Swallowing, speech, and pain symptoms (Time frame: prior to first dose of study treatment and at the time of last follow up to 5 years)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as April 2021

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate for solution for infusion vial (25mg/ml) costs £2,630, and 50mg powder for concentrate for solution for infusion vial costs £1,315.[22]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Head and neck cancer – contusugene ladenovec (ID76). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Head and neck cancer - intensity modulated radiotherapy (ID15). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab for treating recurrent or metastatic squamous cell head and neck cancer after platinum-based chemotherapy (ID1231). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab for untreated recurrent or metastatic squamous cell carcinoma of the head and neck (ID1140). Expected date of issue February 2020
- NICE technology appraisal. Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (TA490). November 2017.
- NICE technology appraisal guidance. Cetuximab for treating recurrent of metastatic squamous cell cancer of the head and neck (TA473). August 2017.
- NICE clinical guideline. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36). June 2018.
- NICE quality standard. Head and neck cancer (QS146). March 2017.
- NICE cancer service guideline. Improving outcomes in head and neck cancers (CSG6). November 2004.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Head and Neck (Adult). B16/S/a
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- 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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- Scottish Intercollegiate Guidelines Network. Diagnosis and management of head and neck cancer. A national clinical guideline. 2006.[26]

ADDITIONAL INFORMATION

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