NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# May 2024

# Pembrolizumab adjuvant therapy for locally advanced cutaneous squamous cell carcinoma

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

| NIHRIO ID: 20578 | NICE ID: Not Available | UKPS ID: 665185 |
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## Licensing and Market Availability Plans

Currently in phase III clinical development

## Summary

Pembrolizumab is in development for the adjuvant treatment of patients with high-risk locally advanced cutaneous squamous cell carcinoma (cSCC) following surgery and radiotherapy. cSCC is a type of skin cancer that develops in the outermost layer of the skin. Certain factors can increase an individual's risk of developing cSCC, such as exposure to the sun, fair skin, history of sunburn, and immune conditions. Because of this, cSCC is usually present on areas of skin that are commonly exposed to the sun, such as the head, neck, and forearms. Locally advanced cSCC can appear raised and rough as well as having the tendency to bleed easily and cause disfiguration. Locally advanced means that the tumour has spread to the deeper layers of skin or nearby lymph nodes and as a result there are limited treatment options. Adjuvant therapies are given to patients following surgery and radiotherapy to reduce the risk of the cancer returning.

Pembrolizumab is a type of immunotherapy that is given intravenously (into the vein). It functions to block a protein called PD-1 that some cancer cells use to avoid being detected by the immune system. This can enable the immune system to recognise and attack cancer cells. If licenced, pembrolizumab will provide the first adjuvant (treatment to reduce the risk of the cancer returning once removed) treatment option for those with locally advanced cSCC who have already had surgery and radiotherapy.

## Proposed Indication

Adjuvant treatment of adults with high risk, locally advanced, cutaneous, squamous cell carcinoma (cSCC) following surgery and radiation.[1]

## Technology

### Description

Pembrolizumab (KEYTRUDA, MK-3475) 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 an inhibitory receptor of T-cell activity that has been shown to be involved in the control of T-cell immune responses.[2] Tumour cells can use the PD-1 pathway in order to evade the T cells so they can grow and spread.[3] Pembrolizumab therefore works by blocking the inhibitory signal that contributes to a reduced immune response and as a result causes a shift towards enhancing immune reactivity and anti-tumour responses.[4,5]

Pembrolizumab is currently in clinical development for the adjuvant treatment of adults with high-risk locally advanced cSCC, previously treated with surgery and radiation. In the phase III trial (KEYNOTE-630, NCT03833167), participants are given 400 mg of pembrolizumab by intravenous (IV) infusion on day one of a 42-day cycle for up to nine cycles. Participants that complete nine cycles of pembrolizumab and experience biopsy-proven-disease recurrence may be eligible to receive up to 18 additional cycles of pembrolizumab in an open-label design.[1]

### Key Innovation

Individuals who are diagnosed and treated for a squamous cell skin lesion have an increased risk of developing a second lesion in the same location or a nearby skin area, with most recurrences developing within two years after the completion of treatment.[6,7] Due to the high risk of recurrence, there is a high level of unmet need for these patients who currently have no approved adjuvant therapies available to them. Recent data suggest that programmed death 1 inhibitors such as pembrolizumab may provide a well-tolerated, effective, and durable response in patients with locally advanced cSCC and therefore address the unmet needs of patients.[8] In the phase II trial (NCT03284424) adjuvant pembrolizumab was shown to have robust antitumour activity for locally advanced cSCC with a 50% objective response rate and a complete response rate of 16.7%.[8,9] If licenced, pembrolizumab will become the first adjuvant treatment option to patients with locally advanced cSCC who have undergone full resection and radiotherapy.

### Regulatory & Development Status

Pembrolizumab currently has Marketing Authorisation in the EU/UK for the following:[2]

- Melanoma
- Non-small cell lung carcinoma
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Microsatellite instability high or mismatch repair deficient cancers
- Oesophageal carcinoma
- Triple-negative breast cancer
- Endometrial carcinoma
- Cervical Cancer
- Gastric or gastro-oesophageal junction adenocarcinoma

Pembrolizumab is currently in phase II and III clinical development for: [10]

- Ovarian cancer
- Fallopian tube cancer

- Bladder cancers
- Colorectal cancers
- Lymphomas
- Liver cancers
- Prostate cancer
- Biliary tract cancer
- Small cell lung cancer
- Breast neoplasms

## Patient Group

### Disease Area and Clinical Need

Skin cancer is divided into two main non-melanoma types, basal cell carcinoma and squamous cell carcinoma (SCC), which is also referred to as cSCC. cSCC is a type of skin cancer that develops from keratinocyte cells in the outer layer of the skin called the epidermis.[11,12] High-risk cutaneous squamous cell carcinoma represents a subgroup of this disease, where patients are at higher risk of metastasis and death.[13] Locally advanced cSCC is when the cancer has spread to deeper layers of skin or nearby lymph nodes.[14] cSCCs are fast growing and develop in areas of the skin exposed to the sun which have been previously burnt, on scars, or that have been ulcerated for a long time. These areas typically include parts of the head, neck, and on the back of the hands and forearms.[11] cSCCs vary in their appearance but usually they appear scaly/crusty, raised and rough as they originate from the outer layer of the skin and can also cause disfiguration as the tumour advances. The cSCC may be sore/tender and in some cases, there may be an ulcer beneath the cSCC causing it to bleed easily. cSCC is not an inherited cancer, however inherited characteristics such as fair skin and tendency to burn can increase an individual's risk of developing the disease. Others at an increased risk of developing locally advanced cSCC include those who work outdoors, older people with a lifetime of exposure to the sun, immunosuppressed individuals and people with skin conditions such as albinism and xeroderma pigmentosum.[15]

cSCC is the second most common type of skin cancer in the UK accounting for approximately 23 out of every 100 skin cancer cases.[11,15] There are approximately 25,000 cSCC cases diagnosed per year in the UK, with one study reporting the age-standardized incidence rate of cSCC in the UK between 2013-2015 as 77 per 100,000 person-years.[16,17] Most cases are detected early and are easy to treat but roughly 5% of cases progress into locally advanced or metastatic disease.[12] In England (2022-23), there were 709 finished consultant episodes (FCE) (ICD-10 code: C44, 'Other malignant neoplasm of the skin', which includes both SCC and basal cell carcinoma) and 128,249 admissions, resulting in 124,544 day cases and 18,263 FCE bed days.[18]

### Recommended Treatment Options

There are currently no NICE recommended adjuvant treatment options for locally advanced cSCC.

## Clinical Trial Information

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| Trial | **MK-3475-630/KEYNOTE-630**; NCT03833167, 2018-001974-76; A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pembrolizumab Versus Placebo as Adjuvant Therapy Following Surgery and Radiation in Participants With High-risk Locally Advanced Cutaneous Squamous Cell Carcinoma<br>**Phase III** – Active, not recruiting |

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| | **Locations(s)**: 10 EU countries, UK, USA, and other countries.<br>**Primary completion date:** May 2025 |
| Trial Design | Randomised, parallel assignment, double-blind, placebo-controlled |
| Population | N=430; subjects with histologically confirmed locally advanced cSCC that have been assessed as disease free following surgery and radiotherapy; aged 18 years and over. |
| Intervention(s) | 400 mg pembrolizumab by intravenous (IV) infusion on day 1 of each 42-day cycle for up to 9 cycles |
| Comparator(s) | Matched placebo |
| Outcome(s) | Primary outcome:<br>• Recurrence free survival which was defined as the time between the date of randomisation to the date of first local or regional recurrence of the index lesion, distant metastasis, or death due to any cause; whichever occurred first up to approximately 60 months.<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The cost of a vial of pembrolizumab 100mg/4ml concentrate for solution for infusion has an NHS indicative price of £2,630.00.[19]

## Relevant Guidance

### NICE Guidance

- NICE quality standard. Skin cancer (QS130). January 2024

### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/s/b
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS Northern England. Strategic Clinical Networks: NECN Skin Cancer Clinical Guidelines. May 2016

### Other Guidance

- Newlands C, Currie R, Memon A, Whitaker S, Woolford T. Non-melanoma skin cancer: United Kingdom National Multidisciplinary Guidelines. 2016.[20]
- British Association of Dermatologists. British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020. 2020.[21]

## Additional Information

# References


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