Health Technology Briefing
May 2024

Pembrolizumab neoadjuvant therapy and as adjuvant therapy with radiotherapy for previously untreated stage III/IVA head and neck squamous cell carcinoma

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28856	NICE ID: Not available	UKPS ID: 674273

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab is in clinical development as neoadjuvant therapy (given before surgery to shrink a tumour) and in combination with standard of care radiotherapy as adjuvant therapy (given after surgery) for the treatment of locally advanced head and neck squamous cell carcinoma (HNSCC). HNSCC is a cancer that develops in the mucous membranes of the mouth, nose or throat. Locally advanced cancers are cancers that have spread from where they started to nearby tissue or lymph nodes. Locally advanced HNSCC outcomes are poor and recurrence rates are high with radiotherapy as neoadjuvant and/or adjuvant therapy. Current chemotherapy options cause severe adverse events in many patients. Therefore, there is an urgent need for new effective treatments to improve patient outcomes.

Pembrolizumab is a monoclonal antibody (protein) that stimulates the body's immune system by triggering T-cells (a type of white blood cells) to find and kill cancer cells. Pembrolizumab is administered intravenously (into a vein). Radiotherapy destroys cancerous cells by using ionising radiation to damage the cell's DNA leading to cell death. If licensed, pembrolizumab, given before surgery, and after surgery with radiotherapy would improve the effectiveness of surgical intervention for patients with locally advanced HNSCC.

Proposed Indication

For neoadjuvant therapy and in combination with standard of care radiotherapy as adjuvant therapy for newly diagnosed Stage III/IVA resectable locoregionally advanced head and neck squamous cell carcinoma (LA HNSCC).[1]

Technology

Description

Pembrolizumab is a humanised monoclonal immunoglobulin (Ig) G4 antibody which binds human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1), causing potential immune checkpoint inhibitory and antineoplastic 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 ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on adenomatous polyposis coli (APCs). Activated PD-1 negatively regulates T-cell activation and plays a key role in tumour evasion from host immunity.[2,3]

Pembrolizumab neoadjuvant therapy and in combination with standard of care radiotherapy (with or without cisplatin) as adjuvant therapy, is currently in clinical development for the treatment of Stage III-IVA resectable LA HNSCC in treatment naïve patients. In the phase III clinical trial (KEYNOTE-689; NCT03765918), participants receive 200 mg of pembrolizumab via intravenous (IV) infusion on day 1 of each 21-day cycle for 2 cycles as a neoadjuvant prior to surgery. For adjuvant therapy following surgical resection, high risk participants receive 200 mg pembrolizumab (IV) on day 1 every three weeks for fifteen 21-day cycles plus standard of care radiotherapy, with the addition of cisplatin (IV) 100 mg/m^2 on day 1 every three weeks for three 21-day cycles. Low risk participants, following surgical resection, receive 200mg pembrolizumab (IV) on day 1 every three weeks for fifteen 21-day cycles plus standard of care radiotherapy as adjuvant therapy.[1]

Key Innovation

Standard of care treatment for LA HNSCC causes severe acute toxicity in more than three quarters of patients, resulting suboptimal cumulative dose and dose intensity in some patients, which leads to compromising outcomes.[4] Patients with resected LA HNSCC have a one-year disease-free survival (DFS) rate of 65%–69% despite adjuvant (chemo)radiotherapy. When neoadjuvant and adjuvant pembrolizumab is added to standard-of-care (chemo) radiotherapy, one-year DFS is estimated at 97% and 66% in patients with intermediate-risk and high-risk, resected HNSCC, respectively[5]. In a phase II clinical trial, neoadjuvant and adjuvant pembrolizumab was shown to increase one-year DFS rate in intermediate-risk HNSCC patients relative to historical control.[5] Preoperative treatment with pembrolizumab and chemotherapy in resectable LA HNSCC has a high pathological complete response rate with no significant impact on surgical safety, and has been found to also increase the rate of laryngeal function preservation.[6]

If licensed, pembrolizumab neoadjuvant therapy, and in combination with standard of care radiotherapy as adjuvant therapy, would provide an additional treatment option for newly diagnosed Stage III-IVA resectable LA HNSCC.

Regulatory & Development Status

Pembrolizumab has Marketing Authorisation in the EU/UK for the following indications:[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
- Biliary tract carcinoma

Pembrolizumab is also in phase II/III clinical development for several indications, some of which include:[7]

- Ovarian cancer
- Thyroid cancer
- Advanced solid tumors
- Anal cancer
- Hepatocellular cancer
- Non-muscle invasive bladder cancer

Patient Group

Disease Area and Clinical Need

Head and neck cancer is a general term that covers different cancers that start in the tissues in the head and neck area, including the oral cavity, pharynx (throat – includes nasopharynx, oropharynx and hypopharynx) and larynx (voice box).[8] 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 typically develops in the mucous membranes of the mouth, nose and throat.[9] HNSCC is caused by a variety of factors including tobacco use 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, particularly in younger people.[9] The symptoms of HNSCC may include a lump in the neck or a sore in the mouth or throat 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 and, paralysis of the muscles in the face, or pain in the face, chin or neck.[10]

In England in 2017, there were a total of 7,587 registrations of malignant neoplasm of the lip, oral cavity and pharynx (ICD-10 codes C00-C14) which equates to a directly age-standardised rate of 20.1 cases per 100,000 males and 9.3 cases per 100,000 females.[11] Overall, malignant neoplasm of the lip, oral cavity or pharynx accounted for roughly 2.5% of cancer registrations for that year.[11] In England in 2022-23, there were 30,516 finished consultant episodes (FCE), and 27,675 admissions with a primary diagnosis of malignant neoplasm of the lip, oral cavity or pharynx (ICD-10 codes C00-C14), resulting in 17,297 day cases and 79,575 FCE bed days.[12] Head and neck cancer is the 8th most common cancer in the UK. Incidence rates in the UK for head and neck cancer are highest in people aged 70-74 (2016-2018). Over the last decade, incidence rates in the UK have increased by almost a sixth (16%).[13] In the UK between 2017-2019, there were 4,143 deaths from head and neck cancer. The European age-standardised mortality rates per 100,000 of the population are 3.5 in females and 10.2 in males.[14]

Recommended Treatment Options

NICE recommends the following treatment options for LA HNSCC:[15]
• For squamous cell carcinoma of the larynx:
  ○ radiotherapy with concomitant chemotherapy;
  ○ surgery with adjuvant radiotherapy, with or without concomitant chemotherapy.
• For squamous cell carcinoma of the hypopharynx:
  ○ larynx-preserving treatment if radiation and neo-adjuvant and/or concomitant chemotherapy would be suitable;
  ○ radiotherapy with neo-adjuvant and/or concomitant chemotherapy if larynx-preserving treatment is suitable;
  ○ primary surgery followed by adjuvant radiotherapy if chemotherapy is not a suitable treatment;
  ○ adjuvant radiotherapy to people having surgery as their primary treatment, including concomitant chemotherapy if appropriate.

Clinical Trial Information

Trial	**KEYNOTE-689**; NCT03765918; 2017-001139-38; A Phase III, Randomised, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC) **Phase III:** Active, not recruiting **Location(s):** 9 EU countries, UK, USA, Canada and other countries **Primary completion date:** September 2025
Trial Design	Randomised, parallel assignment, open-label
Population	N=704 (estimated); aged 18 years and older; participants with histologically confirmed new diagnosis of resectable, non-metastatic, squamous cell carcinoma that is either: Stage III Human Papillomavirus (HPV) positive oropharyngeal primary that is tumour size (T) 4, lymph node involvement (N) 0-2, no distant metastases (M0); Stage III or IVA oropharyngeal HPV negative; or Stage III or IVA larynx/hypopharynx/oral cavity primaries,
Intervention(s)	• Neoadjuvant therapy: pembrolizumab 200mg (IV) on day 1 of each 21-day cycle for 2 cycles • Adjuvant therapy (high risk participants): pembrolizumab 200mg (IV) on day 1 every 3 weeks (Q3W) for fifteen 21-day cycles + standard of care radiotherapy + cisplatin 100 mg/m^2 (IV) on day 1 Q3W for three 21-day cycles (following pembrolizumab neoadjuvant therapy) • Adjuvant therapy (low risk participants): pembrolizumab 200mg (IV) on day 1 Q3W for fifteen 21-day cycles plus standard of care radiotherapy (following pembrolizumab neoadjuvant therapy)
Comparator(s)	• No neoadjuvant therapy • Adjuvant therapy (high risk participants): standard of care radiotherapy + cisplatin 100 mg/m^2 (IV) on day 1 Q3W for three 21-day cycles • Adjuvant therapy (low risk participants): standard of care radiotherapy

Outcome(s)	Primary outcome measure: Event-free Survival (EFS) [Time frame: up to approximately 80 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 25mg vial (100mg/4ml) costs £2,630.[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Atezolizumab for adjuvant treatment of high-risk locally advanced squamous cell head and neck cancer (ID4052). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Leukocyte interleukin in combination for neoadjuvant treatment of resectable locally advanced squamous cell head and neck cancer (TS ID 10203). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Xevinapant with platinum-based chemotherapy and radiotherapy for untreated locally advanced squamous cell head and neck cancer (ID6199). Expected date of issue to be confirmed.
- NICE clinical guideline. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36). February 2016. Last updated June 2018.
- NICE quality standard. Head and neck cancers (QS146). March 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Head and Neck (Adult). B16/S/a
- 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

- Spanish Society of Medical Oncology (SEOM). SEOM clinical guidelines for the treatment of head and neck cancer. 2021.[17]
- European Society for Medical Oncology (ESMO). Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[18]
- The Journal of Laryngology & Otology. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines. May 2016.[19]

Additional Information

References

1 ClinicalTrials.gov. *Study of Pembrolizumab Given Prior to Surgery and in Combination With Radiotherapy Given Post-surgery for Advanced Head and Neck Squamous Cell Carcinoma (MK-3475-689). Trial ID: NCT03765918*. 2023. Status: Ongoing. Available from: https://clinicaltrials.gov/study/NCT03765918#study-overview [Accessed 6/3/24].

2 Electronic Medicines Compendium (emc). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. Available from: https://www.medicines.org.uk/emc/product/2498/productinfo#about-medicine [Accessed 6/3/24].

3 NIH National Cancer Institute. *Pembrolizumab*. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/pembrolizumab?redirect=true [Accessed 6/3/24].

4 Noronha V JA, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A, Murthy V, Gupta T, D'Cruz AK, Banavali S, Pai PS, Chaturvedi P, Chaukar D, Pande N, Chandrasekharan A, Talreja V, Vallathol DH, Mathrudev V, Manjrekar A, Maske K, Bhelekar AS, Nawale K, Kannan S, Gota V, Bhattacharjee A, Kane S, Juvekar SL, Prabhash K. Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. *Journal of Clinical Oncology*. 2018;36(11):1064-72. Available from: https://doi.org/10.1200/JCO.2017.74.9457.

5 Wise-Draper TM GS, Palackdharry S, Hinrichs BH, Worden FP, Old MO, Dunlap NE, Kaczmar JM, Patil Y, Riaz MK, Tang A, Mark J, Zender C, Gillenwater AM, Bell D, Kurtzweil N, Mathews M, Allen CL, Mierzwa ML, Casper K, Jandarov R, Medvedovic M, Lee JJ, Harun N, Takiar V, Gillison M. Phase II Clinical Trial of Neoadjuvant and Adjuvant Pembrolizumab in Resectable Local-Regionally Advanced Head and Neck Squamous Cell Carcinoma. *Clinical Cancer Research*. 2022;28(7):1345-52. Available from: https://doi.org/10.1158/1078-0432.CCR-21-3351.

6 Wang K GL, Lu H, He X, Li D, Liu C, Liu S and Wang X. Efficacy and safety of pembrolizumab with preoperative neoadjuvant chemotherapy in patients with resectable locally advanced head and neck squamous cell carcinomas. *Frontiers in Immunology*. 2023;14:1189752. Available from: https://doi.org/10.3389/fimmu.2023.1189752.

7 ClinicalTrials.gov. *Filtered search for ongoing Pembrolizumab trials* Available from: https://clinicaltrials.gov/search?intr=Pembrolizumab&aggFilters=phase:2%203,status:not%20rec%20act%20enr [Accessed 26/3/24].

8 Macmillan Cancer Support. *Head and neck cancer*. 2022. Available from: https://www.macmillan.org.uk/cancer-information-and-support/head-and-neck-cancer [Accessed 26/3/24].

9 MedlinePlus. *Head and neck squamous cell carcinoma*. Available from: https://medlineplus.gov/genetics/condition/head-and-neck-squamous-cell-carcinoma/ [Accessed 26/3/24].

10 NIH National Cancer Institute. *Head and Neck Cancers*. Available from: https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet#:~:text=Head%20and%20neck%20cancer%20symptoms%20may%20include%20a%20lump%20in,by%20other%2C%20less%20serious%20conditions. [Accessed 26/3/24].

11 Office for National Statistics. *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 6/3/24].

12 NHS-Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23.

13 Cancer Research UK. *Head and neck cancers statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers#heading-Zero [Accessed 6/3/24].

14 Cancer Research UK. *Head and neck cancers mortality statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers/mortality#heading-Zero [Accessed 26/3/24].

15 National Institute for Health and Care Excellence (NICE). *Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over*. 2016. Available from: https://www.nice.org.uk/guidance/ng36/chapter/Recommendations [Accessed 6/3/24].

16 National Institute for Health and Care Excellence (NICE). *Pembrolizumab [Specialist drug] Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/pembrolizumab-specialist-drug/medicinal-forms/#solution-for-infusion [Accessed 26/3/24].

17 Mesia R IL, Lambea J, Martínez-Trufero J, Soria A, Taberna M, Trigo J, Chaves M, García-Castaño A, Cruz J. SEOM clinical guidelines for the treatment of head and neck cancer (2020). *Clinical & Translational Oncology*. 2021;23(5):913-21. Available from: https://doi.org/10.1007/s12094-021-02582-0.

18 Machiels JP RLC, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2020;31(11):1462-75. Available from: https://doi.org/10.1016/j.annonc.2020.07.011.

19 Paleri V RN. Introduction to the United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer. *The Journal of Laryngology & Otology* 2016;130(S2):7-228. Available from: https://doi.org/10.1017/S0022215116000359.

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