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HEALTH TECHNOLOGY BRIEFING JANUARY 2021

Pembrolizumab for recurrent or metastatic nasopharyngeal cancer

NIHRIO ID	30301	**NICE ID**	10530
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	659265

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

SUMMARY

Pembrolizumab is in clinical development for the treatment of patients with platinum pre-treated recurrent or metastatic nasopharyngeal cancer (NPC). NPC is a rare type of cancer that affects the part of the throat connecting the back of the nose to the back of the mouth (the pharynx). It is often difficult to distinguish the symptoms of NPC from less serious conditions and many people do not have any symptoms until the cancer reaches an advanced stage. Therefore, there is a medical need for effective treatments for advanced nasopharyngeal cancer.

Pembrolizumab is an immunotherapy drug administered by intravenous (IV) infusion. It works by improving the activity of white blood cells (T-cells) by blocking a protein, PD-L1, thereby increasing the ability of the immune system to kill cancer cells. If licenced, pembrolizumab could provide an additional treatment option for patients with platinum pre-treated recurrent or metastatic nasopharyngeal cancer.

PROPOSED INDICATION

Treatment of patients with platinum pre-treated recurrent or metastatic NPC.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands programmed cell death ligand 1 and 2 (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]

In the phase III trial (NCT02611960), participants will receive 200 mg of pembrolizumab IV on day 1 of each 3-week cycle until progressive disease or unacceptable toxicity or a maximum of up to 35 cycles.[1]

INNOVATION AND/OR ADVANTAGES

Current treatment for recurrent/metastatic NPC that progresses on a platinum-based regimen is limited.[3]

In NPC, prolonged exposure to Epstein-Barr virus leads to increased expression of programmed death 1 (PD-1), resulting in suppressed T-cell immunity and tumour surveillance. Pembrolizumab is a monoclonal anti–PD-1 antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. In the phase 1b KEYNOTE-028 study, pembrolizumab was associated with an overall response rate of 22% in mostly heavily pre-treated patients with NPC.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced in the UK:[2]

- As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- As monotherapy for the adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection.
- As monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ⩾ 50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations.
- As monotherapy for the treatment of locally advanced or metastatic NSCLC 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 pembrolizumab.
- As monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

- As monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- As 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 monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ⩾ 1.
- As monotherapy for the treatment of recurrent or metastatic HNSCC 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 (RCC) in adults.

A positive CHMP opinion was received in December 2020 for pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.[4]

The most common adverse events of pembrolizumab monotherapy include: anaemia, hyperthyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema and pyrexia.[2]

Pembrolizumab is currently in phase III and phase II clinical trials for many other cancer indications including gastric, cervical, head and neck, urothelial and breast cancer.[5]

PATIENT GROUP

DISEASE BACKGROUND

Nasopharyngeal cancer is a rare type of cancer that affects the part of the throat connecting the back of the nose to the back of the mouth (the pharynx). It is distinguished from other types of cancer that also affect the throat, such as laryngeal cancer and oesophageal cancer.[6] Cancer that spreads from where it started to a distant part of the body is called metastatic cancer.[7] Cancer that has recurred is cancer that has come back, usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumour or to another place in the body.[8]

The exact cause of nasopharyngeal cancer is unknown. Factors can increase the risk of developing the condition include exposure to the Epstein-Barr virus, family history, diet high in salt-cured foods and occupational exposure to hardwood dust. Nasopharyngeal cancer is more common in some ethnic groups living in the UK. For example, in people of south Chinese or north African descent. It is also more common in men than women.[6]

Symptoms of nasopharyngeal cancer can include: a lump in the neck, hearing loss (usually only in 1 ear), tinnitus, a blocked or stuffy nose, nosebleeds. It is often difficult to distinguish these symptoms from less serious conditions and many people with nasopharyngeal cancer do not have any symptoms until the cancer reaches an advanced stage.[6]

CLINICAL NEED AND BURDEN OF DISEASE

Cancer of the nasopharynx is rare in Europe, with an annual crude incidence rate of 1.1 per 100,000.[9] In the UK, about 250 people are diagnosed with nasopharyngeal cancer each year.[6]

In 2019/20 there were 1,563 hospital admissions with primary diagnosis malignant neoplasm of nasopharynx (ICD-10 code C11), and 1,692 finished consultant episodes (FCEs), resulting in 2,758 FCE bed days.[10]

The outlook for nasopharyngeal cancer depends on age, general health and how advanced the condition is when diagnosed. Overall, about 50 out of every 100 people (50%) diagnosed with nasopharyngeal cancer will live for five years or more after diagnosis. Survival rates are better for younger people, but worse for older people. Around 70 out of 100 (70%) people under 45 years of age, and 35 out of 100 (35%) people aged 65 to 74, will live for five years or more after being diagnosed with nasopharyngeal cancer.[11]

In England and Wales in 2019, there were 145 deaths with malignant neoplasm of malignant neoplasm of nasopharynx (ICD-10 code C11) recorded as the underlying cause.[12]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The optimal treatment strategy of patients with advanced NPC should be discussed in a multidisciplinary team. Radiation therapy (RT) is the mainstay of treatment and is an essential component of curative-intent treatment of non-disseminated NPC. Stage I disease is treated by RT alone, while stage III, IVA, IVB disease are treated by RT with concurrent chemotherapy. In metastatic NPC, palliative chemotherapy should be considered for patients with adequate performance status. Platinum combination regimens are commonly used as first-line therapy since cisplatin represents the most effective drug.[9]

CURRENT TREATMENT OPTIONS

NICE guidance states people with locally advanced (stage II and above) nasopharyngeal cancer should be offered intensity-modulated radiation therapy with concomitant chemotherapy. Adjuvant or neo-adjuvant chemotherapy for people with locally-advanced (stage II and above) nasopharyngeal cancer should be considered.[13]

PLACE OF TECHNOLOGY

Treatment of patients with platinum pre-treated recurrent or metastatic nasopharyngeal cancer.

CLINICAL TRIAL INFORMATION

Trial	**MK-3475-122/KEYNOTE-122;** NCT02611960; A Two-arm, Open-label, Randomized Phase III Study of Pembrolizumab (MK-3475) Monotherapy Versus Standard Chemotherapy in Platinum Pre-treated, Recurrent or Metastatic Nasopharyngeal Cancer (NPC) (Keynote-122) **Phase III** - Active, not recruiting **Location(s):**

	Canada, Hong Kong, Republic of Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, and United States[a] **Primary completion date:** November 2020
Trial design	Randomised, parallel assignment, open label
Population	N=233, aged 18 years and older, metastatic or incurable locally recurrent, non-keratinizing differentiated NPC or undifferentiated NPC, previously treaded with platinum therapy.
Intervention(s)	Pembrolizumab 200 mg IV on Day 1 of each 3-week cycle until progressive disease or unacceptable toxicity or a maximum of up to 35 cycles.
Comparator(s)	Standard of care chemotherapy comprising of docetaxel, capecitabine or gemcitabine (as per KN-122 protocol)
Outcome(s)	Primary outcome(s); • Overall Survival (OS) [Time Frame: Up to approximately 2 years] 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 for solution for infusion vial (25mg/ml) costs £2,630.00.[14]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36). June 2018.

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: Radiotherapy (All Ages). B01/S/a

OTHER GUIDANCE

- SEOM clinical guideline in nasopharynx cancer. 2017.[15]
- Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines. 2016.[16]
- Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012.[9]

[a] Information provided by Merck Sharp & Dohme Ltd

ADDITIONAL INFORMATION

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.