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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Nivolumab in combination with chemoradiotherapy for squamous cell head and neck cancer

NIHRIO ID	26625	**NICE ID**	10459
Developer/Company	Bristol Myers Squibb	**UKPS ID**	657410

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Nivolumab in combination with cisplatin-based chemoradiotherapy (cisplatin-RT) is currently in development for the adjuvant treatment of high-risk patients with metastatic squamous cell carcinoma of the head and neck (HNSCC) following surgery to remove the cancer. HNSCC is a cancer of the mouth, nose or throat that develops in the squamous cells found in the outer layer of skin and the mucous membranes that line body cavities such as the airways and intestines. Patients with high-risk disease have an increased chance of the cancer returning following surgical resection. There is a need to develop additional treatment options to prevent recurrence of the cancer in these patients.

Nivolumab, is a human monoclonal antibody which belongs to a class of drugs known as immune checkpoint inhibitors. When given by intravenous administration, nivolumab blocks the activity of a protein called PD-1 which improves the activity of T-cells (a type of white blood cell) thereby increasing the ability of the immune system to kill cancer cells. If licenced, nivolumab in combination with cisplatin-RT would offer an additional treatment option for locally advanced HNSCC patients with a high-risk of recurrence.

PROPOSED INDICATION

Treatment of patients with squamous cell carcinoma of the head and neck (HNSCC).[1]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo, BMS-936558) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. These are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment which in turn results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses through blockade of PD-1 binding to PD-L1 and PD-L2. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2]

Nivolumab in combination to (cisplatin-RT) is currently in clinical development for the adjuvant treatment of locally advanced, high-risk HNSCC. In the phase III clinical trial (NIVOPOSTOP, NCT03576417) participants will receive (via intravenous (IV) administration): 240mg of nivolumab 3 weeks prior to RT-cisplatin; 360mg of nivolumab on days 1, 22, and 43 of RT-cisplatin; and 480mg nivolumab for maintenance.[1]

INNOVATION AND/OR ADVANTAGES

Expression of PD-1 is identified in approximately 85% of HNSCC cases. Nivolumab is a PD-1 directed immunotherapy and has demonstrated single-agent activity in HNSCC, leading to multicentre phase Ib, II and III trials defining new standards of care in recurrent or metastatic HNSCC.[3]

HNSCC presents as locally advanced disease in a majority of patients and is prone to relapse despite aggressive treatment. Immune checkpoint inhibitors (ICI) have shown clinically significant efficacy in patients with recurrent/metastatic HNSCC. Preclinical data has showed the synergistic role of concurrently administered ICIs and chemoradiotherapy.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab as a combination therapy currently has Marketing Authorisation in the EU/UK for the following indications:[2]

- In combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumours have no sensitising EGFR mutation or ALK translocation
- In combination with ipilimumab for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma
- In combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma
- In combination with cabozantinib for the first-line treatment of adult patients with advanced renal cell carcinoma

- In combination with ipilimumab for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy

Across all tumour types the most frequently reported adverse reactions (≥ 10%) occurring in patients taking nivolumab monotherapy are fatigue (29%), rash (17%), pruritus (13%), diarrhoea (13%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).[2]

Nivolumab in combination with cisplatin-RT is also in phase III development for NSCLC and HPB mediated (p16-postitive) oropharyngeal carcinoma; and phase II development for several other cancer indications including: cervical cancer, oropharynx cancer, nasopharyngeal carcinoma, breast cancer, and oesophageal squamous cell carcinoma.[5]

PATIENT GROUP

DISEASE BACKGROUND

Head and neck cancer is a general term that covers many different types of cancer, including the oral cavity, pharynx (throat – includes nasopharynx, oropharynx and hypopharynx) and larynx (voice box).[6] Squamous cell carcinoma of the head and neck (SCCHN) 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. SCCHN typically develops in the mucous membranes of the mouth, nose and throat.[7]

SCCHN 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 SCCHN. HPV infection accounts for the increasing incidence of SCCHN in younger people.[7]

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 and, paralysis of the muscles in the face, etc.[8]

In addition to the life-threatening nature of SCCHN, 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.[9]

CLINICAL NEED AND BURDEN OF DISEASE

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). This equates to a directly age-standardised rate of 20.1 cases per 100,000 males and 9.3 cases per 100,000 females. Overall, malignant neoplasm of the lip, oral cavity or pharynx accounted for roughly 2.5% of cancer registrations for that year.[10] In England in 2019-20, there were 29,596 finished consultant episodes (FCE), and 26,773 admissions with a primary diagnosis of malignant neoplasm of the lip, oral cavity or pharynx (ICD-10 codes C00-C14), resulting in 15,363 day cases and 77,077 FCE bed days.[11]

Statistics from Cancer Research UK report that in 2017, head and neck cancer was the 8th most common cancer in the UK. Head and neck cancer disproportionately affects men, where it is the 4th most common cancer, whilst in females, it is the 13th most common. The majority of head and neck cancers occurs in the larynx. Incidence rates in the UK for head and neck cancer are highest in people aged 70-74 (2015-2017) and in England, it more commonly affects people living in deprived areas. Over the last decade, incidence rates in the UK have increased by more than a fifth (22%).[12]

In the UK in 2018, there were 4,078 deaths from head and neck cancer. The European age standardised mortality rates per 100,000 of the population was 3.6 in females and 9.9 in males.[13] Over 83.9% of people diagnosed with cancer of the larynx in England survive their disease for 1 year or more (2013-2017) and over half (63.9%) survive their disease for 5 years or more (2013-2017).[14]

Survival varies by head and neck cancer subtype in England and is highest in salivary glands cancer and lowest in hypopharyngeal cancer (one-, five- and ten-year survival, 2009-2013). Head and neck cancers survival in England is generally higher for people diagnosed aged 15-49 compared with other age groups, though the association varies with subtype.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

People with HNSCC are usually treated in specialist centres by a team of specialist healthcare professionals. For most people, the aim of treatment is to remove or destroy all of the cancer, reduce the chances of it coming back (recurring), and reducing the long-term effects of treatment[16]. The treatment you are offered depends on: where the cancer is located; the cancer stage; the size of the tumour and the general health of the patient. Treatment for head and neck cancers can include: surgery, chemotherapy, radiotherapy and targeted therapies.[17]

CURRENT TREATMENT OPTIONS

NICE currently does not have any published guidance for the adjuvant treatment of high-risk HNSCC following surgical resection.[18]

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with cisplatin based chemoradiotherapy will offer an additional adjuvant treatment option for patients with locally advanced HNSCC who have undergone surgical resection and have a high-risk of cancer recurrence.

CLINICAL TRIAL INFORMATION

Trial	**NIVOPOSTOP**, NCT03576417; A Phase III Randomized Trial of Post-operative Adjuvant Nivolumab and Concomitant Chemo-radiotherapy in High-risk Patients With Resected Squamous Cell Carcinoma of Head and Neck **Phase III** – Recruiting

	Location: France **Estimated primary completion date:** December 2021
Trial design	Randomised, open-label, parallel assignment, controlled
Population	N=680; adults aged between 18 and 75 years; histologically proven HNSCC from one or more of the following primary sites: oral cavity, oropharynx, hypopharynx or larynx; HNSCC treated by primary surgery; stage III or IV histopathological classification; complete macroscopic resection and recovery from the surgical procedure allowing for cisplatin-RT; currently free of disease but with a high risk of relapse; adequate tumour specimen from archived or resected tissue available for PD-L1, TILs and immune landscape and other biomarker evaluation
Intervention(s)	• 100mg/m^2 cisplatin (IV administration) on days 1, 22, and 43 of radiotherapy • Nivolumab (IV administration) - 240mg 3 weeks before RT-cisplatin - 360mg on days 1, 22, and 43 of RT-cisplatin - 480mg for maintenance
Comparator(s)	100mg/m^2 cisplatin (IV administration on days 1, 22, and 43 of radiotherapy (RT-cisplatin)
Outcome(s)	Primary outcome measure: • Disease free survival [Time frame: 3 years after the end of radiotherapy] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Nivolumab is already marketed in the UK. The NHS indicative prices for nivolumab solution for infusion vials are as follows:[19]

- Nivolumab 100mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1097.00 (Hospital only).
- Nivolumab 240mg/24ml concentrate for solution for infusion (1 vial) (Bristol Myers Squibb Pharmaceuticals Ltd) costs £2633.00 (Hospital only).
- Nivolumab 40mg/4ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £439.00 (Hospital only).

RELEVANT GUIDANCE

NICE GUIDANCE

- 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.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/13 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: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- The Journal of Laryngology and Otology. Head and Neck Cancer: United Kingdom Multidisciplinary Guidelines. 2016.[20]
- European Society for Medical Oncology (ESMO). Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2010.[21]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 90. Diagnosis and Management of Head and Neck Cancer. 2006.[22]

ADDITIONAL INFORMATION

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