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Nivolumab (Opdivo) with ipilimumab (Yervoy) for recurrent, metastatic, squamous cell head and neck cancer – first line

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LAY SUMMARY

Head and neck cancer is the fourteenth most common cancer in the UK. It refers to different types of cancer that begin inside the neck or head, such as mouth cancer or throat cancer. Head and neck cancers usually develop in the squamous cells that line the moist, mucosal surfaces inside the head and neck. Head and neck cancers are often curable if diagnosed at an early stage. Risk factors include smoking tobacco and drinking alcohol. Symptoms may present as hoarseness, difficulty swallowing, pain in the ear and others. Treatment options usually involve chemotherapy or radiotherapy and focus on symptom relief and prolonging life rather than curing.

Nivolumab is a type of protein designed to attach to a certain type of white blood cells called the T cells. T cells are part of the immune system needed to attack the cancer. Nivolumab acts to improve the activity of T cells, thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab is another type of protein that acts in a different way to increase the activity of T cells. If licenced, nivolumab in combination with ipilimumab will offer additional treatment option to prolong lives of this patient group.

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TARGET GROUP

Head and neck cancer (squamous cell, recurrent/metastatic, platinum refractory) – first line; in combination with ipilimumab

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo) is a fully human monoclonal antibody directed against the negative immunoregulatory human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1/PCD-1) with immuno-potentiation activity.[1] The drug molecule is a type of protein that has been designed to recognise and attach to a specific structure. Nivolumab attaches to the PD-1 receptor which is found on certain cells of the immune system called T cells. Cancer cells can produce proteins (PD-L1 and PD-L2) that inhibits this receptor and switch off the activity of the T cells, preventing them from attacking the cancer. By attaching to the PD-1 receptors, nivolumab prevents PD-L1 and PD-L2 from switching off the T cells, thereby increasing the ability of the immune system to kill the cancer cells.[2]

Ipilimumab (Yervoy) is a monoclonal antibody that has been designed to attach to and block the activity of a protein called CTLA-4 (cytotoxic T lymphocyte associated antigen 4) found on the surface of T cells, a type of white blood cell. CTLA-4 inhibits the activity of T cells. Ipilimumab, by blocking CTLA-4, leads to the activation and spread of the T cells, which infiltrate tumours and kill the tumour cells.[3,1]

Clinical trials do not specify the treatment dose and duration of nivolumab with ipilimumab for head and neck cancer, however, it is proposed that Nivolumab is administered by intravenous infusion 480mg over 30 minutes every four weeks.[4,5,19]

Nivolumab in combination with ipilimumab is already registered for metastatic melanoma in the EU, Canada and USA[1]. Nivolumab as a monotherapy is already being used in the EU for:[6]

- Melanoma
- Non-small cell lung cancer
- Renal cell carcinoma
- Classical Hodgkin lymphoma
- Squamous cell cancer of the head and neck
- Urothelial carcinoma.

Adverse effects for nivolumab may include fatigue, lymphocytopenia, low sodium, shortness of breath, musculoskeletal pain, decrease appetite, cough and others.[7] Side effects for ipilimumab may include intestinal problems, liver problems, skin problems, nerve problems, hormone gland problems and eye problems.[8]

INNOVATION and/or ADVANTAGES

If licensed, nivolumab in combination with ipilimumab will offer an additional treatment option for squamous cell head and neck cancer. As shown in clinical trials, this treatment has already proven to prolong overall survival for patients with second line treatment of this combination.[2,3]

DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd

PATIENT GROUP

BACKGROUND

Head and neck cancers usually develop in the squamous cells that line the moist, mucosal surfaces inside the head and neck, often referred to as squamous cell carcinomas of the head and neck.[10] More than 90% of head and neck cancers are squamous cell carcinomas.[9] Head and neck cancers may also begin in the salivary glands, however, this type is relatively uncommon. Salivary glands contain many different types of cells that can become cancerous, hence, there are many different types of salivary gland cancer.[10] Head and neck cancer can also be classified by which part of the body the cancer develops. There are more than 30 different head and neck cancers, such as mouth cancer, laryngeal cancer, throat cancer, salivary gland cancer, nose and sinus cancer or nasopharyngeal cancer.[11]

If diagnosed early, cancers of the head and neck are often preventable or curable. However, patients often present with advanced disease that is incurable or requires aggressive treatment. Risk factors of head and neck cancer include smoking, drinking alcohol, and poor diet.[9] It is said that 75% of head and neck cancers are caused by tobacco and alcohol use. Another risk factor is infection with cancer-causing types of human papillomavirus (HPV), especially HPV type 16. Causes of head and neck cancer might also be preserved or salted foods, poor oral hygiene, occupational exposure, radiation exposure, or Epstein-Barr virus infection.[10]

In most patients, platinum based chemotherapy is used and has demonstrated survival advantages. However, treatment options are limited once platinum based therapy has failed. This platinum-refractory disease is defined as cancer with documented tumour progression during platinum-based treatment or recurrence within 6 months after platinum-based chemotherapy. These patients suffer from a more aggressive form of the cancer and worse outcomes compared to the platinum eligible subgroup.[12]

Symptoms can present as hoarseness, difficulty swallowing, pain in the ear, enlargement of a cervical lymph node, or systemic metastases. Stopping smoking and drinking less alcohol is the most effective way to increase prevention. Early detection improves the outcome of treatments.[9]

CLINICAL NEED and BURDEN OF DISEASE

In 2014, there were 11,449 new cases of head and neck cancer in the UK, which accounts to 3% of all cancer cases in the UK. It is the eighth most common cancer in the UK, whereby it is the fourth most common cancer in males and the twelfths most common cancer in females. Since the 1990s, the head and neck cancer incidence rates in the UK increased by 30%. The crude incidence rate shows that there are 25 new head and neck cancer cases for every 100,000 males in the UK, and 11 for every 100,000

females. This type of cancer is strongly related to age, with the highest incidence rate being in people aged 65 and over. More than half (62%) of head and neck cancers are diagnosed at an advanced stage III or IV. One year net survival among head and neck cancer subtypes is highest in salivary glands cancer and lowest in hypopharyngeal cancer. For all types, one year survival falls between 1 and 5 years after diagnosis. In 2009 to 2013 it was estimated that between 19% and 59% survive head and neck cancer for 10 years or more.[13,14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy (ID971). Expected November 2017
- NICE technology appraisal in development. Head and neck cancer – intensity modulated radiotherapy (ID15). Expected TBC
- NICE technology appraisal. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma (TA462). July 2017
- NICE technology appraisal. Nivolumab for previously treated advanced renal cell carcinoma (TA417). November 2016
- NICE technology appraisal. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016
- NICE technology appraisal. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). February 2016
- NICE technology appraisal. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). July 2014
- NICE technology appraisal. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012
- NICE technology appraisal. Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck (TA172). June 2009
- NICE technology appraisal. Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (TA145). June 2008
- NICE quality standard. Head and neck cancer (QS146). March 2017
- NICE cancer service guidelines. Improving outcomes in head and neck cancers (CSG6). November 2004

NHS ENGLAND and POLICY GUIDANCE

- NHS England. National Cancer Drugs Fund list. V1.31. 15 June 2017.
- 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

Paleri V, Roland N. Head and Neck Cancer – United Kingdom National Multidisciplinary Guidelines. The Journal of Laryngology & Ontology, Vol 130 (S2), 2016

CURRENT TREATMENT OPTIONS

Once diagnosed, staging is an attempt to find out whether or how far the cancer has spread. This may involve an examination under anaesthesia, x-rays and other imagining procedures, and laboratory tests. This helps to find the most appropriate treatment plan, which depends on a number of factors including the exact location of the tumour, stage of cancer, and the person's general health and age.[15]

Both surgery ad radiotherapy are used for the treatment of head and neck cancer, whereby in general, function is better after radiotherapy than surgery, but treatment time for surgery is shorter. Inoperable disease may be treated with combinations of chemotherapy and radiotherapy. In advanced stages outcomes are usually poor, and focus is put on treating the symptoms of a patient rather than curing the disease.[9] Drugs approved by the US FDA for the treatment of head and neck cancer are:[15]

- Bleomycin
- Cetuximab (also approved by EMA for this indication)[16]
- Docetaxel (also approved by EMA for this indication)[17]
- Hydrea
- Keytruda
- Methotrexate
- Nivolumab

It is suggested that fit patients who are symptomatic from their recurrent or metastatic disease should be considered for platinum-based, multi-agent regimes that combine cytotoxic chemotherapy with cetuximab. Single agent chemotherapy regimens are appropriate for many asymptomatic patients with a low burden of disease. Platinum-resistant patients should be treated with cetuximab-based regimen, either alone or in combination with paclitaxel. Targeted therapy may include epidermal growth factor receptor (EGFR) inhibitor therapies. EGFR is commonly expressed in squamous cell head and neck cancer and overexpression is associated with poorer prognosis. Cetuximab is a monoclonal antibody to the EGFR to be routinely used in targeted therapy. Palliative radiation therapy is used to relief symptoms of patients with recurrent disease. Supportive care, such as pain specialists, is recommended.[18]

EFFICACY and SAFETY

Trial	CheckMate 714, NCT02823574, nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo; phase II
Sponsor	Bristol-Myers Squibb
Status	Ongoing, recruiting participants
Source of Information	Trial registry[19]
Location	11 EU countries (incl UK), USA, and other countries

Design	Randomised, active-controlled
Participants	N=315 (planned); aged >= 18 years; Two patient subgroups will be enrolled into CheckMate 714: • Platinum-refractory: patients with Squamous cell carcinoma of the head and neck (SCCHN) that has recurred during or less than six months after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment for locally advanced disease • Platinum-eligible: patients with SCCHN who are platinum-naïve or with disease that has recurred six months or more after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment for locally advanced disease
Schedule	Participants are randomised to a specified dose of nivolumab and ipilimumab on specified days and an active comparator of nivolumab and ipilimumab-placebo.
Follow-up	Not reported
Primary Outcomes	Overall response rate (ORR) in platinum refractory subgroup
Secondary Outcomes	Progression-free survival (PFS) in platinum eligible and refractory subgroups Overall survival (OS) in platinum eligible and refractory subgroups Duration of response (DOR) in platinum eligible subgroup
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date February 2018. Estimated study completion date October 2020.

ESTIMATED COST and IMPACT

COST

Nivolumab is already marketed in the UK; the list price of nivolumab is £439 per 4 ml (40 mg) vial and £1,097 per 10 ml (100 mg) vial.[20]

Ipilimumab is already marketed in the UK; the list price of ipilimumab is £3,750 per 10 ml (50 mg) vial and £15,000 per 40 ml (200 mg).[21]

Both drugs have patient access schemes.[22]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs

☒ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

UK PharmaScan ID: 641505

Bristol-Myers Squibb Pharmaceuticals Ltd

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