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HEALTH TECHNOLOGY BRIEFING
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Nivolumab in combination with ipilimumab for oesophageal squamous cell carcinoma – first line

NIHRIO ID	13755	**NICE ID**	9956
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	645157

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Nivolumab in combination with ipilimumab is in clinical development for patients with advanced, recurrent or metastatic oesophageal squamous cell cancer that has not been treated previously. Advanced oesophageal cancer begins in the food pipe and spreads to other parts of the body. Squamous cell cancers develop from the cells that make up the inner lining of the oesophagus. Symptoms include difficulty swallowing, persistent acid indigestion or heartburn, weight loss, pain in the throat, and chronic cough. Lifestyle factors are attributed to most oesophageal cancers, including smoking and being overweight.

Nivolumab and ipilimumab are immune therapy medicinal products that are currently licensed as a combination treatment of advanced cancers such as melanoma and kidney cancer. Nivolumab works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab works in a different way but also to increase the activity of T-cells. It is thought that when used together, both drugs may be more effective than each on its own. Both drugs given by injection and the combination may offer a treatment option for patients with advanced, recurrent or metastatic oesophageal squamous cell carcinoma who have not been treated previously.

PROPOSED INDICATION

Unresectable advanced, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma in patients 18 years and older.[1]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo) is a human immunoglobulin G4 (IgG4) monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with 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. Engagement of PD-1 with the ligands 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, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including antitumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[2]

Ipilimumab (Yervoy) is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoral T-effector/ T-regulatory cell ratio which drives tumour cell death.[3]

Nivolumab in combination with ipilimumab is currently in development for the treatment of previously untreated advanced oesophageal squamous cell carcinoma. In the phase III clinical trial (2016-001514-20; NCT03143153), nivolumab and ipilimumab are administered via intravenous infusion. The combination is administered in a ratio of 1:4 (nivolumab 10 mg/ml: ipilimumab 40mg/ml.[1,4] Nivolumab is administered at a dose of 3mg/kg as a 30-minute infusion every 2 weeks and ipilimumab 1mg/kg as a 30 minute infusion every 6 weeks.[a]

INNOVATION AND/OR ADVANTAGES

Advanced oesophageal cancer cannot usually be cured and current treatments are used to control and relieve symptoms.[5] Oesophageal cancer can be resistant to systemic treatments and there are no (PD-1)/ (PD-L1) immunotherapies currently licensed to treat this condition.[6]

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition resulted in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.[2]

Therefore the combination of nivolumab plus ipilimumab may be effective in improving survival and may provide a novel first line treatment option for those with advanced oesophageal squamous cell carcinoma.

[a] Information provided by Bristol-Myers Squibb

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab in combination with ipilimumab has Market Authorisation in the EU/UK for the treatment of:[2,3]

- advanced (unresectable or metastatic) melanoma in adults;
- renal cell carcinoma.

The most common adverse reactions (affecting more than one in ten people) associated with treatment with nivolumab in combination with ipilimumab are: hypothyroidism, decreased appetite, headache, dyspnoea, colitis, diarrhoea, vomiting, nausea, abdominal pain, rash, pruritus, arthralgia, fatigue and pyrexia.[2,3]

Nivolumab in combination with ipilimumab is currently in development for the treatment of various types of cancers including breast, ovarian and gastric cancers.[7]

PATIENT GROUP

DISEASE BACKGROUND

Squamous cell cancers develop from the cells that make up the inner lining of the oesophagus. They tend to develop in the upper and middle part of the oesophagus, which is part of the digestive system, however, a cancer can develop anywhere along the length of the oesophagus.[8,9]If the cancer is advanced it means it has spread to another part of the body. The most common types of oesophageal cancer, accounting for over 95% of cases, are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Cancers in the upper oesophagus are nearly always squamous cell cancers as are most cancers in the middle of the oesophagus.[9]

Symptoms of oesophageal cancer include difficulty swallowing, persistent acid indigestion or heartburn, weight loss, regurgitation of food; pain in the throat or behind the breastbone, hoarseness, chronic cough, vomiting blood, and dark stool.[10]

Ninety percent of oesophageal cancer cases are attributed to lifestyle factors, such as being overweight or obese, smoking or using tobacco, alcohol consumption and not eating enough fruit and vegetables. Oesophageal cancer occurs most commonly amongst older people, with 80% of occurrences being in people aged 60 years or older. Although the risk is small, Barrett's oesophagus (a condition in which the cells lining the oesophagus have become abnormal) increases the risk with 1-5% of people with the condition developing oesophageal cancer. Achalasia is also a contributing factor, it is a rare condition in which the valve between the oesophagus and stomach does not relax, causing a blockage in the oesophagus, preventing food and liquid to pass through.[11]

As advanced cancer cannot usually be cured, treatment is used to control it and relieve symptoms. Radiotherapy or chemotherapy may shrink the cancer or stop it growing. Some treatments can help to swallow more easily if the cancer is blocking the food pipe.[5]

CLINICAL NEED AND BURDEN OF DISEASE

Oesophageal cancer is the 13th most common cancer in the UK, accounting for 3% of all new cases, with around 7 in 10 being diagnosed at a late stage. In England in 2016 there were 7,561 new cases of oesophageal cancer, whereby 5,237 occurred in men and 2,324 in women. The directly age-standardised incidence rate shows that there are 22.6 new oesophageal cancer cases for every 100,000 males in the UK, and 8.3 for every 100,000 females.[12] Between 2014 and 2035, the European age-standardised incidence rates for oesophageal cancer (ICD-10 code C15) are projected to decrease from 18.06 per 100,000 (8,919 observed cases) to 17.56 per 100,000 (12,657.3 projected cases).

Oesophageal cancer is strongly related to age, with the highest incidence rates being in older men and women. On average oesophageal cancer is diagnosed in people aged 70 years and over. Age specific incidence rates rise sharply from around age 45-49 years, with the highest rates in the over 90 age group.[13]

In England in 2017/2018 there were 31,131 hospital admissions with a primary diagnosis of malignant neoplasm of oesophagus (ICD-10 code C15), resulting in 89,115 bed days and 22,397 day cases.[14]

Oesophageal cancer is the 7th most common cause of cancer deaths in the UK.[15] In the UK in 2017 there were a total of 6,905 registrations of deaths due to Malignant neoplasm of oesophagus (IDC-10 C.15), of which 4,812 were men.[16] European age-standardised mortality rates between 2014 and 2035 are projected to decrease from 15.77 per 100,000 (equivalent to 7,790 observed cases) to 13.17 per 100,000 (9,747.95 projected cases).[17] 44% of men survive oesophageal cancer for at least one year, and this is predicted to fall to 16% surviving for five years. For women the survival is slightly lower at one year (38%) but similar at five years (15%). Out of the 20 most common cancers in England and Wales, ten-year survival for oesophageal cancer ranks 3rd lowest overall. However, survival has tripled in the last 40 years from 4% to 12% predicted to survive their disease for ten years or more.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Curative (surgical resection) options are currently only available to those where the cancer is localised to the oesophagus or stomach. If investigations reveal that the cancer is advanced and spread to other organs, curative treatment is not possible. Where food blockages occur, a self-expanding metal stent can be placed to relieve this.[19]

Unresectable advanced oesophageal is currently treated through the use of radiotherapy and palliative chemotherapy.[20,21]

CURRENT TREATMENT OPTIONS

For advanced squamous cell oesophageal carcinoma the current treatment goal is palliative. At first line, NICE guidelines advise the following possible drug combinations:[20]

- Doublet treatment: 5-flourouracil or capecitabine in combination with cisplatin or oxaliplatin. These are in use in UK clinical practice, however these do not have current market authorisation for advanced oesophageal carcinoma.
- Triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin. Epirubicin does not have current market authorisation for oesophageal carcinoma although it is in use in UK clinical practice.

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with ipilimumab would offer an additional first line treatment option for advanced (metastatic and/or unresectable) oesophageal squamous cell carcinoma.

CLINICAL TRIAL INFORMATION

Trial	NCT03143153, **EudraCT 2016-001514-20; Nivolumab in combination with ipilimumab or fluorouracil and cisplatin versus fluorouracil and cisplatin; phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial registry;[1,4] Company
Location	EU (incl. UK), USA, Canada and other countries
Design	Randomised, active-controlled, open label, parallel assignment
Participants	n=939 (planned); aged ≥18 years old; advanced (unresectable, recurrent or metastatic) previously untreated oesophageal squamous cell carcinoma.
Schedule	Nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30-minute infusion every 6 weeks
Follow-up	Treatment with nivolumab in combination with ipilimumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity.
Primary Outcomes	• Overall survival (OS) in subjects with PD-L1 expressing tumours. [Time Frame: Approximately 49 months from time first patient is randomized] • Progression-free Survival (PFS) (as 1 assessed by blinded independent central review committee {BICR}) in subjects with PD-L1 expressing tumours. [Time Frame: Approximately 33 months from time first patient is randomized]
Secondary Outcomes	• Overall survival (OS) in All Randomized subjects. [Time Frame: Approximately 49 months from time first patient is randomized] • Progression-free Survival (PFS) in all Randomized Subjects. [Time Frame: Approximately 33 months from time first patient is randomized] Objective Response Rate (ORR). [Time Frame: Approximately 33 months from time first patient is randomized] As assessed by BICR in subjects with PD-L1 expressing tumours and all randomised subjects.
Key Results	Company is awaiting results
Adverse effects (AEs)	Company is awaiting results
Expected reporting date	Primary completion date reported as May 2020

ESTIMATED COST

Nivolumab is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[22]

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

Ipilimumab is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[23]

- Yervoy 200mg/40ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £15000.00 (Hospital only).
- Yervoy 50mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £3750.00 (Hospital only).

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018
- NICE quality standard. Oesophago-gastric cancer (QS176). December 2018
- NICE interventional procedure guidance. Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus (IPG497). Published July 2014
- NICE interventional procedure guidance. Minimally invasive oesophagectomy (IPG407). Published September 2011
- NICE interventional procedure guidance. Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia (IPG355). Published September 2010
- NICE interventional procedure guidance. Palliative photodynamic therapy for advanced oesophageal cancer (IPG206). Published January 2007

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy Proposition: 18F-flourodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) as part of radical radiotherapy treatment planning for oesophageal cancer (all ages). Published date to be confirmed.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and Gastric (Adult). B11/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

- Lordick F, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[24]

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