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HEALTH TECHNOLOGY BRIEFING
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Nivolumab in combination with cisplatin and fluorouracil for oesophageal cancer – first-line

NIHRIO ID	27093	**NICE ID**	10260
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	651905

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

SUMMARY

Nivolumab in combination with cisplatin and fluorouracil is in clinical development for patients with unresectable, advanced, recurrent or metastatic oesophageal squamous cell cancer cell carcinoma. 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 administered by intravenous infusion, works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Cisplatin and fluorouracil are both standard chemotherapies that are used in treating many different types of advanced or metastatic cancers. If licensed, nivolumab in combination with cisplatin and fluorouracil may offer an additional treatment option for patients with advanced, recurrent, unresectable or metastatic oesophageal squamous cell carcinoma.

PROPOSED INDICATION

Treatment of advanced, recurrent, unresectable or metastatic previously untreated squamous cell oesophageal cancer.[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]

Nivolumab in combination with cisplatin and fluorouracil is being developed as first-line treatment for advanced, recurrent, unresectable or metastatic squamous cell oesophageal cancer. In the phase III clinical trial (NCT03143153, CheckMate 648) patients in the experimental arm are given nivolumab in combination with cisplatin and fluorouracil for 49 months.[1]

INNOVATION AND/OR ADVANTAGES

Advanced oesophageal cancer cannot usually be cured and current treatments are used to control and relieve symptoms.[3] Oesophageal cancer can be resistant to systemic chemotherapies. Expression of PDL1/L2 has been associated with a poor prognosis in oesophageal or gastro-oesophageal junction cancer, suggesting that PD-1 inhibition may improve outcomes; there are no (PD-1)/ (PD-L1) immunotherapies currently licensed to treat this condition.[4]

The NICE pathway for the first line treatment of oesophageal cancer recommends a combination of chemotherapies that includes, cisplatin and fluorouracil. The addition of nivolumab, a PD-L1 inhibitor which is not currently recommended for this indication, may offer an additional treatment option.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab in combination with cisplatin and fluorouracil is not licensed in the UK for any indication.

The most common side effects with nivolumab (which may affect more than 1 in 10 people) include tiredness, diarrhoea, nausea (feeling sick), rash and itching, pain in joints, muscles and bones, and hypothyroidism (an underactive thyroid gland), most of which are mild to moderate in severity. Nivolumab is also commonly associated with side effects related to the activity of the immune system on body organs. Most will go away with appropriate treatment or on stopping nivolumab.[6]

PATIENT GROUP

DISEASE BACKGROUND

Oesophageal cancer is a cancer of the gullet (oesophagus). It develops when abnormal cells in the oesophagus grow in an uncontrolled way. Most people are over the age of 60 years when they are diagnosed.[7]

Cancer can develop in any part of the oesophagus. In the upper and middle part of the oesophagus, cancers tend to be squamous cell carcinomas, which develop from cells that make up the inner lining of the oesophagus. Cancers in the lower part tend to be a type of cancer called adenocarcinoma, which tend to start in gland cells. The lower end of the oesophagus that joins the stomach is called the gastro oesophageal junction.[7]

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.[8]

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.[9]

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.[10]

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.[3]

CLINICAL NEED AND BURDEN OF DISEASE

Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cases, with around 7 in 10 being diagnosed at a late stage.[11] In England in 2017 there were 7,569 new cases of oesophageal cancer, whereby 5,280 occurred in men and 2,289 in women. The directly age-standardised incidence rate shows that there were 22.2 new oesophageal cancer cases for every 100,000 males in the UK, and 8.1 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 among men are between 65 and 69 years and among women between 75 and 79 years..[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 (IDC10 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]

Forty-four percent 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.[3,20]

CURRENT TREATMENT OPTIONS

For advanced squamous cell oesophageal carcinoma the current treatment goal is palliative.[5]

According to ESMO guidelines, chemotherapy for metastatic oesophageal cancer is indicated for palliative treatment in selected patients. In squamous cell carcinoma the value of palliative chemotherapy is less proved compared to adenocarcinoma.[21]

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with cisplatin and fluorouracil may offer an additional treatment option for patients with advanced, recurrent, unresectable or metastatic oesophageal squamous cell carcinoma.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 648, NCT03143153, EudraCT 2016-001514-20, CA209-648; pts aged 18 yrs and older; nivolumab in combination with cisplatin and fluoruracil; phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing

Source of Information	Trial registry[1,22]
Location	EU countries (incl UK), USA, Canada and other countries.
Design	Randomised, parallel assignment, open-label
Participants	n=939 (planned); aged 18 and older yrs; oesophageal cancer; squamous cell carcinoma; unresectable, advanced, recurrent and/or metastatic; previously untreated
Schedule	Pts in the experimental arm are given nivolumab in combination with cisplatin and fluorouracil for the duration of treatment.
Follow-up	Active treatment duration: 24 mths in absence of disease progression or unacceptable toxicity.[a]
Primary Outcomes	• Overall survival (OS) [Time frame: Approximately 49 mths from time first pt is randomised] • Progression-free Survival (PFS) [Time frame: Approximately 33 mths from time first pt is randomised]
Secondary Outcomes	• Overall survival (OS) [Time Frame: Approximately 49 months from time first patient is randomized] • Progression-free Survival (PFS) [Time frame: Approximately 33 mths from time first pt is randomised] • Objective Response Rate (ORR) [Time frame: Approximately 33 mths from time first pt is randomised]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date May 2020.

ESTIMATED COST

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

- 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).

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for treating unresectable advanced oesophageal cancer when standard chemotherapy has failed (ID1249). Expected date of publication: September 2020.

[a] Information provided by Bristol-Myers Squibb

- NICE interventional procedure guidance. Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus (IPG497). July 2014.
- NICE interventional procedure guidance. Minimally invasive oesophagectomy (IPG407). September 2011.
- NICE interventional procedure guidance. Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia (IPG355). September 2010.
- NICE interventional procedure guidance. Palliative photodynamic therapy for advanced oesophageal cancer (IPG206). 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

- European Society of Medical Oncology. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[21]

ADDITIONAL INFORMATION

REFERENCES

1 Clincaltrial.gov. *A Study to Evaluate Efficacy in Subjects With Esophageal Cancer Treated With Nivolumab and Ipilimumab or Nivolumab Combined With Fluorouracil Plus Cisplatin Versus Fluorouracil Plus Cisplatin (CheckMate 648). Trial ID: NCT03143153.* Available from: https://clinicaltrials.gov/ct2/show/NCT03143153 [Accessed 29 July 2019].

2 electronic Medicines Compendium. *OPDIVO 10 mg/mL concentrate for solution for infusion.* 2019. Available from: https://www.medicines.org.uk/emc/medicine/30476 [Accessed 11 February 2019].

3 Cancer Research UK. *Oesophageal Cancer – Advanced Cancer.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/advanced-cancer/about-advanced-cancer [Accessed 18 March 2019].

4 Walsh EM, Kelly RJ. Single agent anti PD-1 inhibitors in esophageal cancer—a first step in a new therapeutic direction. *Journal of Thoracic Disease*. 2018;10(3):1308-13. Available from: doi: 10.21037/jtd.2018.03.43 https://dx.doi.org/10.21037%2Fjtd.2018.03.43

5 (NICE). NIfHaCE. *NICE Pathways: Palliative management for people with oesophageal and gastric cancer.* Available from: https://pathways.nice.org.uk/pathways/oesophageal-and-gastric-cancer#path=view%3A/pathways/oesophageal-and-gastric-cancer/palliative-management-for-people-with-oesophageal-and-gastric-cancer.xml&content=view-index [Accessed 20 August 2019].

6 British National Formulary. *Nivolumab.* Available from: https://bnf.nice.org.uk/drug/nivolumab.html#sideEffects [Accessed 25 September 2019].

7 Cancer Research UK. *About oesophageal cancer.* Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/about [Accessed 24 June 2019].

8 Macmillan Cancer Support. *Types of oesophageal cancer* 2019. Available from: https://www.macmillan.org.uk/information-and-support/oesophageal-gullet-cancer/understanding-cancer/types-oesophageal-cancer.html [Accessed 11 February 2019].

9 Cancer Research UK. *Oesophageal Cancer – Symptoms.* Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/symptoms [Accessed 10 January 2019].

10 Cancer Research UK. *Oesophageal cancer – causes and risks.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/causes-risks [Accessed 10 January 2019].

11 Cancer Research UK. *Oesophageal cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer#heading-Zero [Accessed 3 July 2019].

12 Office for National Statistics. *Cancer Registration Statistics, England, 2017.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Downloaded 11 February 2019].

13 Cancer Research UK. *Oesophageal cancer incidence statistics.* 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence%20-%20heading-Seven [Accessed 10 January 2019].

14 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18: Procedures and Interventions.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18

15 Cancer Research UK. *Oesophageal cancer mortality statistics.* 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/mortality [Accessed 10 January 2019].

16 Office for National Statistics. *Death registration summary tables - England and Wales 2017.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Downloaded 11 February 2019].

17 Cancer Research UK. *Cancer Research UK - Selected Cancers, Number of Projected and Observed Deaths and European Age-Standardised Mortality Rates, by Cancer Type and Sex.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ [Downloaded 29 January 2019].

18 Cancer Research UK. *Oesophageal cancer survival statistics.* 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/survival#heading-Zero [Accessed 11 January 2019].

19 The Oesophageal Patients Association. *Oesophagogastric Cancer - The Patient's Pathway.* 2019. Available from: https://www.opa.org.uk/the-patients-pathway.html [Accessed 11 February 2019].

20 National Institute for Health and Care Excellence. *NICE guideline (NG83): Oesophago-gastric cancer: assessment and management in adults.* 2019. Available from: https://www.nice.org.uk/guidance/ng83/chapter/Recommendations [Accessed 11 February 2019].

21 Lordick F, on behalf of the EGC, Mariette C, on behalf of the EGC, Haustermans K, on behalf of the EGC, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2016;27(suppl_5):v50-v7. Available from: http://dx.doi.org/10.1093/annonc/mdw329 10.1093/annonc/mdw329.

22 EU Clinical Trials Register. *A Study to Evaluate Efficacy in Subjects with Esophageal Cancer Treated with Nivolumab and Ipilimumab or Nivolumab Combined with Fluorouracil plus Cisplatin versus Fluorouracil plus Cisplatin. Trial ID: 2016-001514-20.* Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001514-20/FR [Accessed 14 January 2019].

23 National Institute for Health and Care Excellence. *BNF: Nivolumab: Solution for infusion* Last Update Date: Available from: https://bnf.nice.org.uk/medicinal-forms/nivolumab.html [Accessed 11 February 2019].

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