NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JULY 2019

Nivolumab for oesophageal or gastro-oesophageal junction cancer - adjuvant

NIHRIO ID	12944	**NICE ID**	9743
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	641506

Licensing and market availability plans	Currently in Phase III trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Nivolumab is a medicinal product that is being developed for the adjuvant treatment (after the primary treatment) of patients with resected oesophageal or gastro-oesophageal junction cancer. Oesophageal develops when abnormal cells in the gullet (oesophagus) grow in an uncontrolled way. The lower end of the oesophagus that joins the stomach is called the gastro oesophageal junction. Gastro oesophageal junction (GOJ) cancer develops at the point where the gullet joins the stomach, and is considered a separate type of cancer.

Nivolumab is a type of immunotherapy that is currently licensed in the UK for the treatment of several types of cancers such as melanoma, non-small cell lung cancer, and kidney cancer. Nivolumab works by improving the activity of a type of white blood cells called T-cells through blocking a protein called programmed death -1 (PD-1) on the surface of T-cells and thereby increasing the ability of the immune system to kill cancer cells. If licensed, nivolumab will offer an adjuvant treatment option for patients with resected oesophageal or GOJ cancer, who currently have few effective adjuvant therapies available.

PROPOSED INDICATION

Stage II and III resected oesophageal or gastro-oesophageal junction cancer - adjuvant.[a]

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 the ligands 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 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 anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[1]

Nivolumab is currently being evaluated in a Phase III clinical trial (NCT02743494) for treating patients with resected oesophageal or gastro-oesophageal junction cancers.[2] The treatment schedule and duration were not reported in the trial registry.

INNOVATION AND/OR ADVANTAGES

Currently, no effective adjuvant standard of care is available following resection. Expression of PD-L1/L2 has been associated with a poor prognosis in oesophageal or gastro-oesophageal junction cancer, suggesting that PD-1 inhibition may improve outcomes.[3] Studies have shown that nivolumab, as monotherapy or in combination with other treatments, is successful amongst patients diagnosed with many types of cancers.[4] A phase I/II study of nivolumab monotherapy for chemotherapy-refractory patients with gastric cancer demonstrated tumour regression, a median overall survival (OS) of five months and a 12 month OS rate of 36% in patients with PD-L1+ and PD-L1 tumours. Further, in a phase 3 trial, nivolumab demonstrated an overall survival (OS) benefit vs placebo, resulting in a 37% reduction in the risk of death and double the OS rate at 12 months in patients with gastric cancer refractory to $\geq$ 2 lines of chemotherapy. These results suggest that nivolumab might be an effective standard of care in heavily pre-treated patients with resected oesophageal or gastroesophageal junction cancer.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In the UK, Nivolumab as monotherapy or in combination with other cancer therapies has the following therapeutic indications:

- Melanoma: as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- Adjuvant treatment of melanoma: as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
- Non-Small Cell Lung Cancer (NSCLC): as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.
- Renal Cell Carcinoma (RCC): as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. In combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

[a] Information provided by Bristol-Myers Squibb Pharmaceuticals Ltd on UK PharmaScan

- Classical Hodgkin Lymphoma (cHL): as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.
- Squamous Cell Cancer of the Head and Neck (SCCHN): as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.
- Urothelial Carcinoma: as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (n = 2578) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions ($\geqslant$ 10%) were fatigue (30%), rash (17%), pruritus (13%), diarrhoea (13%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).[4]

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. [6]

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.[6]

Gastro oesophageal junction (GOJ) cancer develops at the point where the oesophagus joins the stomach. Research suggests that GOJ cancer is a separate type of cancer that can behave differently to cancers of the oesophagus and stomach. Cancer is described as GOJ cancer if the centre of the cancer is less than 5cm above or below the GOJ. There are three types of GOJ cancer depending on their location: [7]

- Type 1: the GOJ cancer spreads down into the GOJ from above, so there are cancer cells in the lower part of the oesophagus and GOJ. The cancer's centre is between 1 and 5cm above the junction.
- Type 2: the GOJ cancers develop at the actual GOJ and the cancer's centre is between 1cm and 2cm below the junction.
- Type 3: the GOJ cancer spreads up into the GOJ from below, so there are cells in the top of the stomach and the GOJ. The cancer's centre is between 2 and 5cm below the junction

Oesophageal cancers are more common in men than women, and is particularly more common in older people. On average in the UK, around 40 out of 100 (around 40%) of new cases are in people aged 75 years and over. The condition is very rare in people younger than 40 years.[6] [7] Factors that can increase risks of developing oesophageal cancers include increasing age, lifestyle factors (e.g. smoking or using tobacco, alcohol, diet etc.) and other medical conditions (e.g. achalasia).[8]

CLINICAL NEED AND BURDEN OF DISEASE

Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cancer cases in 2016. Around 7 in 10 oesophageal cancer cases were diagnosed at a late stage in England in 2014.[9] 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.[10]

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 75 years and over. Age specific incidence rates rise sharply from around age 45-49 years, with the highest rates in the 90+ age group.[11]

In England in 2017/2018 there were 31,131 hospital admissions with a primary diagnosis of malignant neoplasm of oesophagus (ICD-10 code C15) and 39,645 finished consultant episodes resulting in 89,115 bed days and 22,397 day cases.[12]

Oesophageal cancer is the 7th most common cause of cancer deaths in the UK.[13] 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.[14] 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).[15] 44% of men survive oesophageal cancer for at least one year, and this is predicted to fall to 16% surviving for five years according to 2010-2011 data in England and Wales. 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, oesophageal cancer survival in the UK survival has tripled in the last 40 years from 4% to 12% predicted to survive their disease for ten years or more.[16]

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.[17] Unresectable advanced oesophageal is currently treated through the use of radiotherapy and palliative chemotherapy.[18,19]

CURRENT TREATMENT OPTIONS

For radical treatment of oesophageal cancer via surgical resection, NICE guideline recommends chemotherapy or chemo-radiotherapy after surgery for people with gastric cancer who did not have chemotherapy before surgery with curative intent.[18]

PLACE OF TECHNOLOGY

If licensed, nivolumab will offer a treatment option as an adjuvant therapy for patients with resected oesophageal or GOJ cancer.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 577,** NCT02743494**,** EudraCT 2015-005556-10**, nivolumab vs placebo; phase III trial**
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial registry[2,20]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo controlled
Participants	N=760 (planned); aged 18 years and older; diagnosed with stage II/III carcinoma of the oesophagus or GOJ; completed pre-operative chemo radiotherapy followed by surgery; diagnosed with residual pathologic disease after being surgically rendered free of disease with negative margins following complete resection
Schedule	No details are reported on the trial registry.
Follow-up	Not reported.
Primary Outcomes	• Disease-Free Survival of adjuvant nivolumab in subjects with resected esophageal cancer or gastroesophageal junction cancer who have received chemoradiotherapy followed by surgery [Time Frame: Approximately 36 months after the first subject is randomized] • Overall Survival of adjuvant nivolumab in subjects with resected esophageal cancer or gastroesophageal junction cancer who have received chemoradiotherapy followed by surgery [Time Frame: Approximately 49 months after the first subject is randomized]
Secondary Outcomes	Overall survival rate [Time Frame: Overall survival rate at 1, 2, and 3 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as Sept 2020. Estimated study completion date reported as October 2024

ESTIMATED COST

Nivolumab (Opdivo) is already marketed in the UK; a 100mg/10mL concentrate for solution for infusion vial costs £1,097, a 240mg/24mL concentrate for solution for infusion vial costs £2,633, and a 40mg/4ml concentrate for solution for infusion vial costs £439.[21]

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
- NICE Guidance. Nivolumab for previously treated oesophageal cancer [ID1249]. Expected publication date July 2020
- NICE Guidance. Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy [TA378]. Published January 2016

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.[22]

ADDITIONAL INFORMATION

REFERENCES

1 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].

2 ClinicalTrials.gov. *An Investigational Immuno-therapy Study of Nivolumab or Placebo in Patients With Resected Esophageal or Gastroesophageal Junction Cancer (CheckMate 577). Trial ID: NCT02743494, CheckMate 577*. Available from: https://clinicaltrials.gov/ct2/show/NCT02743494 [Accessed 24 June 2019].

3 Kelly RJ, Lockhart AC, Jonker DJ, Melichar B, Andre T, Chau I, et al. CheckMate 577: A randomized, double-blind, phase 3 study of nivolumab (Nivo) or placebo in patients (Pts) with

resected lower esophageal (E) or gastroesophageal junction (GEJ) cancer. American Society of Clinical Oncology 2017.

4 European Medicines Agency. *Opdivo.* Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo#authorisation-details-section [Accessed 24 June 2019].

5 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

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

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

8 Cancer Research UK. *Oesophageal cancer: Causes and risks.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/causes-risks [Accessed 3 July 2019].

9 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].

10 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].

11 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].

12 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Downloaded 4th February 2019].

13 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].

14 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].

15 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].

16 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-Two [Accessed 3 July 2019].

17 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].

18 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].

19 Cancer Research UK. *Treatment for advanced cancer.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/treatment/advanced-treatment [Accessed 10th June 2019].

20 Register ECT. *A Randomized, Multicenter, Double Blind, Phase III Study of Adjuvant Nivolumab or Placebo in Subjects with Resected Esophageal, or Gastroesophageal Junction Cancer*. *Trial ID: 2015-005556-10*. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2015-005556-10 [Accessed 24/06/2019].

21 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].

22 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.

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.