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Nivolumab (Opdivo) for Oesophageal Cancer

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LAY SUMMARY

Oesophageal cancer is the 14th most common cancer in the UK, accounting for approximately 2% of all new cancer cases. This type of cancer affects the oesophagus (gullet), which is the long muscular tube that carries food from the throat to the stomach as part of the digestive process.

The most common types of oesophageal cancer, accounting for over 95% of cases, are squamous cell carcinoma and adenocarcinoma. Symptoms of these types of oesophageal cancer include swallowing, persistent acid indigestion or heartburn, weight loss and regurgitation of food. The main risk factors for oesophageal cancer are excessive alcohol consumption, smoking, being overweight or obese, unhealthy diet, increasing age, and having certain other medical conditions. The most common treatment for oesophageal cancer in the UK is surgery; alternative treatments are radiotherapy and chemotherapy.

Nivolumab is a drug which blocks a protein, called the programmed death-1 (PD-1) receptor, on the surface of certain immune cells (called T-cells). By blocking the PD-1 receptor this triggers the T-cells to find and kill cancer cells. Nivolumab is given as a drip directly into a vein in the hand or arm. Studies of nivolumab in this population are currently being conducted to determine if it may extend survival or slow the progression of the disease.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Patients with esophageal Cancer refractory or intolerant to Combination Therapy with Fluoropyrimidine and Platinum-based Drugs.

TECHNOLOGY

DESCRIPTION

Nivolumab [anti-PD-1 MAb, Medarex; anti-PD-1 MAb, Ono; BMS 936558; BMS-936558; MDX-1106; nivolumab; NSC 748726; NSC-748726; ONO 4538; ONO-4538; Opdivo] is a fully-human IgG4 monoclonal antibody which targets and blocks the PD-1 (programmed death-1) receptor on the surface of T-cells. This action triggers a T-cell mediated immune response against cancer cells.[1, 2] Nivolumab is administered by intravenous (IV) infusion at 3mg/kg over 60 minutes every 2 weeks for its currently approved indications.

Nivolumab has been approved/licensed for use in the EU for the following indications:[3]

- Advanced or metastatic (squamous and non-squamous) non-small cell lung cancer
- First and second line advanced unresectable or metastatic melanoma.
- Advanced renal cell carcinoma after prior therapy in adults
- Relapsed or refractory classical Hodgkin's lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin

Recognised common adverse events (>10%) of nivolumab in the currently licenced indications include: neutropenia, diarrhoea, nausea, rash, pruritus (itching), fatigue, increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcaemia, increased creatine, lymphopaenia, leucopoenia, thrombocytopenia, anaemia, hypercalcaemia, hyperkalaemia, hypomagnesaemia and hyponatraemia.[4]

Nivolumab is currently in phase II trials for the following indications:

- Recurrent or metastatic, platinum refractory, squamous cell head and neck cancer (first line)
- Unresectable advanced or recurrent oesophageal or gastroesophageal junction cancer
- Unresectable advanced or recurrent gastric cancer
- Recurrent glioblastoma
- Relapsed small cell lung cancer after platinum based first line chemotherapy
- Advanced Hepatocellular carcinoma
- Urothelial carcinoma
- Advanced or metastatic clear cell renal cell carcinoma who have received prior antiangiogenic therapy
- Relapsed and refractory multiple myeloma
- Unresectable pleural mesothelioma
- Ovarian cancer

Nivolumab is currently in phase III trials for the following indications:

- Prostate cancer

- Peritoneal cancer
- Fallopian tube cancer
- Pancreatic cancer
- Triple negative breast cancer
- B-cell lymphoma
- Diffuse large B-cell lymphoma
- Non-Hodgkin's lymphoma
- Cervical cancer
- Endometrial cancer
- Soft tissue sarcoma

INNOVATION and/or ADVANTAGES

- If licensed, nivolumab will offer an alternative treatment option for a sub-population of those with refractory oesophageal cancer and/or those intolerant to combination therapy with fluoropyrimidine and platinum based drugs.

DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)

AVAILABILITY, LAUNCH or MARKETING

Nivolumab is currently in phase III clinical trials for the treatment of oesophageal cancer.

Nivolumab was awarded PIM status for melanoma by MHRA in January 2015.

Nivolumab is a designated orphan drug in the USA for the following indications:

- Glioblastoma
- Gastric cancer and gastro-oesophageal junction cancer
- Hepatocellular Carcinoma
- Small cell lung cancer
- Stage IIb to stage IV melanoma
- Oesophageal cancer

Nivolumab was designated Breakthrough Therapy by the FDA for treatment for the following indications:

- Unresectable advanced or metastatic urothelial cancer that has progressed on or after a platinum-containing regimen in June 2016
- Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after platinum based therapy in April 2016
- Previously treated patients with non-squamous non-small cell lung cancer in September 2015
- Hodgkin's lymphoma after failure of autologous stem cell transplant and brentuximab in May 2014.
- Previously treated advanced melanoma in September 2014
- Advanced or metastatic renal cell carcinoma in September 2015

Nivolumab was designated fast track status by the FDA for the following indications in April 2013:

- Non-small cell lung cancer
- Melanoma
- Renal Cancer

Nivolumab was designated priority review status by the FDA for the following indications:

- Unresectable advanced or metastatic urothelial cancer that has progressed on or after a platinum-containing regimen in October 2016
- Mismatch repair deficient or microsatellite instability high metastatic colorectal cancer after prior fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy in April 2017
- Advanced squamous non-small cell lung cancer after prior therapy in March 2015
- Classical hodgkins lymphoma after prior therapies in April 2016
- Previously treated advanced melanoma in September 2014
- Previously untreated advanced melanoma in August 2015
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy in November 2015

Nivolumab was designated accelerated approval status by the FDA for the treatment of unresectable or metastatic melanoma who no longer respond to other drugs in January 2015.

PATIENT GROUP

BACKGROUND

Oesophageal cancer affects the oesophagus (gullet) – the long muscular tube that carries food from the throat to the stomach. The oesophagus is part of the digestive system. The walls of the oesophagus contract when swallowing food. The most common types of oesophageal cancer, accounting for over 95% of cases, are squamous cell carcinoma and adenocarcinoma.[5] 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, coughing up blood, and dark stool.[6]

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 eighty percent of occurrences being in people aged 60 years or older.[7] Survival depends on many factors, including health status, cancer sub-type, the nature of treatment received and fitness level. If the cancer hasn't spread, around 40% of patients live for 5 years or more. Between 30 to 40% of individuals with localised oesophageal cancer can have treatment to try to cure it.[8]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, there were 8,779 cases of oesophageal cancer diagnosed in 2013, with an increasing trend.[9] Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cases.

The crude incidence rate shows that there are 19 new oesophageal cancer cases for every 100,000 males in the UK, and 9 for every 100,000 females. The incidence is strongly related to age, with the highest rate in older men and women. Age specific incidence rates rise sharply from around age 45-

49. The highest rates are in the 90+ age group. The incidence rates in the UK have in general increased by 6% since the early 1990s.

Oesophageal cancer patients with a known stage are most commonly diagnosed at stage IV. More patients are diagnosed at a late stage than an early stage.[10]

Worldwide, oesophageal cancer is the eighth most common cancer, with 456,000 new cases diagnosed in 2012.[11]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer [ID1096]. Expected October 2018.
- NICE technology appraisal guidance in development. Nivolumab for previously treated gastric or gastro-oesophageal junction cancer [ID1118]. Expected February 2018.
- NICE technology appraisal guidance. Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy [TA378]. January 2016.
- NICE interventional procedures guidance. Palliative photodynamic therapy for advanced oesophageal cancer (IPG206). January 2007.
- NICE interventional procedures guidance. Photodynamic therapy for early-stage oesophageal cancer (IPG200). December 2006.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and Gastric (Adult). B11/S/a.
- NHS England. Clinical Commissioning Policy: Robotic assisted surgery for oesophagus-gastric cancers. 16006/P. July 2016.

OTHER GUIDANCE

No guidance is currently available.

CURRENT TREATMENT OPTIONS

The most common treatment option for oesophageal cancer in the UK is surgery, especially if the cancer has not spread beyond the oesophagus. Depending on the position of the tumour, the surgeon may need to enter the chest cavity, the abdomen or the neck in order to remove the affected parts.

Another treatment for potential cure is radiotherapy, which is particularly useful for people with early tumour, especially squamous cancer. Radiotherapy can be used in conjunction with surgery. Chemotherapy is sometimes used in cases where surgery and radiotherapy do not show the expected effects. Endoscopic intubation can help to relive difficulties in swallowing.

Endoscopic laser treatment is also possible.[12]

A new approach of treatment is the use of photodynamic therapy, which involves giving the patient a special chemical which enters the cancer cells and is sensitive to certain light wavelengths. When light is passed into the oesophagus using a probe, it activates the chemical which then destroys the cancer. This treatment is currently under investigations in trials.[12]

EFFICACY and SAFETY

Trial	16-174, CA 209-473, CA209473, Checkmate 473, EudraCT Number: 2015-003339-36, IRAS ID 200037, JapicCTI-153026, NCI-2016-01219, NCT02569242, ONO-4538-24, ONO-4538-24/CA209-473, TrialTroveID-265684, U1111-1172-5391, VICCGI15146	JapicCTI-142422, TrialTroveID-202697
Sponsor	Bristol-Myers Squibb, Ono Pharmaceutical	Ono Pharmaceutical
Status	Open.	Closed
Source of Information	Trialtrove	Trialtrove
Location	EU (Incl. UK), United States, Japan, South Korea, Taiwan	Japan
Design	Randomised, efficacy, safety, pharmacokinetics, open label, active comparator, multiple arm	Efficacy, safety, open label, single arm
Participants	Patients with unresectable advanced or recurrent oesophageal cancer. N=390. > or = 20 years old.	Patients with oesophagus cancer who have failed in standard chemotherapies. N=65. Age-range: 49-80. Histological type was squamous in all patients.
Schedule	Patients will be randomised to the standard treatment (docetaxel or paclitaxel) arm or the nivolumab arm. Arm 1: Experimental: Nivolumab Arm Nivolumab 240 mg/body solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends . Assigned Intervetions: Arm 2 Active Comparator Arm (Docetaxel/Paclitaxel) Docetaxel: Intravenously administered at a dose of 75 mg/m2 every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends OR Paclitaxel: Intravenously administered at a dose of 100 mg/m2	Patients receive ONO-4538 at a dose of 3mg/kg IV Q2W ASCO GI 2016: Nivolumab (3mg/kg IV Q2W) was administered to patients until observing unacceptable toxicity or disease progression assessed at 6 week intervals.

	weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.	
Follow-up	Not reported.	Not reported.
Primary Outcomes	Overall survival. Timepoints of evaluation of this end point. The time from randomization until death from any cause.	To study efficacy and safety of ONO-4538 for the treatment of Oesophagus Cancer
Secondary Outcomes	Progression-free survival. Objective response rate. Duration of response.	Response rate. The proportion of patients with a confirmed objective response assessed by independent review committee according to RECIST 1.1 Overall survival, progression-free survival, safety
Key Results	Not reported.	Nivolumab has meaningful activity and a manageable safety profile in pretreated oesophageal cancer.
Adverse effects (AEs)	Not reported.	Not reported.
Expected reporting date	Not reported.	-

Trial	16-197, 20160534, BMS C209-577, CA209-577, CA209577, CheckMate 577, EudraCT Number: 2015-005556-10, IRAS ID: 202286, JapicCTI-163409, NCI-2016-00858, NCT02743494, NL56855.031.16, Reec-2016-2314, S16-00474, TrialTroveID-277028, U1111-1177-2665
Sponsor	Bristol-Myers Squibb, Ono Pharmaceutical
Status	Open.
Source of Information	Trialtrove
Location	EU (Incl. UK), United States and Canada
Design	Randomised, efficacy, safety, placebo control, pharmacokinetics, double blind/blinded, immunogenicity, multiple arm
Participants	Patients with resected oesophageal, or gastroesophageal junction cancer. N= 760. > or = 18 years. Diagnosed with Stage II/III carcinoma of the oesophagus or gastroesophageal junction. 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	Arm 1: Experimental: Nivolumab specified dose on specified days. Arm 2: Placebo Comparator: Placebo specified dose on specified days.
Follow-up	Not reported.
Primary Outcomes	Disease-free survival and overall survival.
Secondary Outcomes	Overall survival rate.

Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	04-2020

Trial	JapicCTI-142656, NCT02267343, ONO-4538-12, TrialTroveID-218773
Sponsor	Ono Pharmaceutical
Status	Completed
Source of Information	Trialtrove
Location	Japan, South Korea, Taiwan
Design	Randomised, efficacy, safety, placebo control, double blind/blinded, superiority, multiple arm
Participants	N=493. > or = 20 years. Patients with unresectable advanced or recurrent gastric cancer (including esophagogastric junction cancer).
Schedule	Experimental: ONO-4538 Arm ONO-4538 3mg/kg solution intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends. Placebo Comparator: Placebo intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends Patients were randomized in a 2:1 ratio to receive 3 mg/kg ONO-4538 (N=330) or placebo (N=163) every 2 weeks until disease progression or severe adverse events occurred.
Follow-up	Not reported.
Primary Outcomes	Efficacy and safety of ONO-4538 in patients with unresectable advanced or recurrent gastric cancer (including esophagogastric junction cancer) refractory to or intolerant of standard therapy.
Secondary Outcomes	Overall survival. Progression-free survival. Objective response rate. Duration of response. Safety. AEs.
Key Results	Nivolumab was effective as the salvage treatment for pretreated AGC with significantly improved OS, PFS and ORR compared to placebo.
Adverse effects (AEs)	Not reported.
Expected reporting date	-

TIMATED COST and IMPACT

COST

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other: improved patient convenience

☐ 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

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