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HEALTH TECHNOLOGY BRIEFING
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Nivolumab in combination with ipilimumab for gastric or gastroesophageal junction cancer – first line

NIHRIO ID	13146	**NICE ID**	9159
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	642274

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Nivolumab in combination with ipilimumab is under development for the treatment of advanced gastric or gastroesophageal junction cancer. Gastric cancer is a malignant tumour originating in the cells of the stomach. Advanced gastric cancer begins in the stomach and spread into the tissues around the stomach, either as locally advanced disease, or it can metastasise to other areas of the body. Advanced cancer cannot usually be cured, but treatment may control further growth of the disease, relieve symptoms and give the patient a good quality of life. Gastric cancer is mainly diagnosed at this latter stage decreasing the likelihood of a positive outcome.

Nivolumab is a human monoclonal antibody, which binds to a protein found on T-cells blocking its reaction with inhibitors (PD-L1/PD-L2) which allows T-cells to kill to cancer cells. Ipilimumab is an immune checkpoint inhibitor that blocks T-cell inhibitory signals increasing the number of reactive T-effector cells. If licensed, this combination could provide a first line treatment that has the potential to improve health outcomes.

PROPOSED INDICATION

Treatment of adult patients with previously untreated advanced or metastatic gastric or gastroesophageal junction cancer.[1]

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 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 which 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. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2]

Ipilimumab (Yervoy, BMS-734016) is a 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 intra-tumoural T-effector/ T-regulatory cell ratio which drives tumour cell death.[3]

Nivolumab in combination with ipilimumab is currently in clinical development for the treatment of advanced or metastatic gastric cancer. In the phase III clinical trial, CheckMate649, participants receive the combination therapy intravenously.[1]

INNOVATION AND/OR ADVANTAGES

This is a new combination for this indication and neither technology is currently licensed for gastric cancer in the UK.

In a phase I/II trial, the combination of nivolumab and ipilimumab demonstrated clinically meaningful antitumor activity, durable responses, encouraging long-term overall survival, and a manageable safety profile in patients with chemotherapy-refractory esophagogastric cancer.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In the UK, nivolumab is currently licensed in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma, in combination with chemotherapy for the first-line treatment of metastatic non-small cell lung cancer and first-line treatment of intermediate/poor-risk advanced renal cell carcinoma in adults.[2,3]

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

Nivolumab in combination with ipilimumab is currently in phase III clinical development for the treatment of various types of cancers including lung, renal, ovarian, cervix, and prostate.[5]

PATIENT GROUP

DISEASE BACKGROUND

Gastric cancer is a malignant tumour originating in the cells of the stomach. There are several different types of stomach cancer. More than 95% of stomach cancers develop in the cells of the stomach lining and are known as adenocarcinomas. This starts in the glandular cells of the stomach lining.[6] Most gastric cancers originate in the gland cells in the inner stomach lining.[7] Advanced gastric cancer begins in the stomach and spread into the tissues around the stomach, either as locally advanced disease, or it can metastasise to other areas of the body such as the liver, lungs, lymph nodes, or the oesophagus. Advanced cancer cannot usually be cured, but treatment may control further growth of the disease, relieve symptoms and give the patient a good quality of life.[6]

The risk of gastric cancer has been associated with consumption of smoked and salted foods and lack of refrigeration. The widespread use of refrigeration has been cited as a reason for the decrease in the incidence of gastric cancer. Several events at the molecular level have been implicated in the development and progression of gastric cancers. Gastric cancer can involve loss of the tumour suppression gene, p53.[8] Gastric cancer begins with a mutation in the structure of the DNA in cells, which can affect how they grow. This means cells grow and reproduce uncontrollably, resulting in a tumour. It is not known what triggers the changes in DNA that lead to gastric cancer. Several other factors increase the risk of gastric cancer such as aging (55 years and older), male gender, smoking, severe chronic atrophic gastritis, peptic ulcers caused by Helicobacter pylori infection, diet, family history of gastric cancer, having another type of cancer, vitamin B12 deficiency, and history of stomach surgery.[9]

Symptoms of gastric cancer include weight loss, abdominal pain, nausea and vomiting and fatigue.[10]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, gastric cancer was the 17th most common cancer in the UK. There were around 6,600 new cases in the UK in 2015-2017. The age-standardised incidence rate in England for malignant neoplasm of the stomach (ICD-10 C16), in 2017, was 9.9 per 100,000.[11] Gastric cancer patients with a known stage are most commonly diagnosed at stage IV (46-57%).[12] The European age-standardised incidence rate of gastric cancer in the UK is projected to decrease from 13.53 per 100,000 cases (equating to 6682 observed cases) in 2014 to 11.26 (equating to 8281 projected cases) in 2035.[13]

In England in 2017, the age-standardised mortality rate for malignant neoplasm of the stomach (ICD-10 code C16) was 6.7 per 100,000.[14] In the 2017 death registration in England and Wales, there were 3,772 deaths (2,444 males, 1,328 males) due to malignant neoplasm of stomach (C16) with the higher proportions in aged 65 and above.[15]

According to 2013-2017 data, 17% of people diagnosed with gastric cancer in England and Wales survive their disease for ten years or more.[16] When diagnosed at stage I, 88% will survive for at least one year; this figure drops to 21% for those diagnosed in stage IV. At stage I, 5-year survival rates are 65%, stage II, 36% and stage III 24%. There is no data for the 5-year survival of stage IV patients. Gastric cancer mortality is strongly related to age, with the highest mortality rates being in older males and females.[17]

In England, in 2019-2020, there were 27,533 finished consultant episodes (FCE) for malignant neoplasm of stomach (ICD 10: C16), resulting in 22,055 hospital admissions and 59,174 FCE bed days.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The most common treatments for gastric cancers are surgery, radiotherapy, and chemotherapy. The patient may have one of these treatments or a combination. If the tumour is in the upper part of the stomach, the patient may also have radiotherapy prior to surgery. If surgery is recommended, the patient may have chemotherapy beforehand. If it is not possible to remove the tumour completely, then the treatment focus will be on preventing the tumour from getting any bigger and causing further harm to the body. This can be done by surgery (palliative surgery) or by chemotherapy. When it is not possible to eliminate the cancer or slow it down, the aim of treatment will be to relieve the symptoms by surgery or radiotherapy.[19,20]

For stomach cancer, chemotherapy might be given to the patient before surgery to reduce the amount of cancer that has to be removed during the operation. Chemotherapy can also be used after surgery to destroy any remaining cancer cells and prevent the cancer from coming back.[20]

CURRENT TREATMENT OPTIONS

NICE recommendation for neoadjuvant and adjuvant treatment include:[21]
People with localised oesophageal and gastro-oesophageal junctional adenocarcinoma (excluding T1N0 tumours) who are going to have surgical resection should be offered a choice of:

- Chemotherapy, before or before and after surgery or
- Chemoradiotherapy, before surgery.

For gastric cancer:

- Chemotherapy before and after surgery to people with gastric cancer who are having radical surgical resection.
- Chemotherapy or chemoradiotherapy after surgery for people with gastric cancer who did not have chemotherapy before surgery with curative intent

PLACE OF TECHNOLOGY

If licensed, nivolumab plus ipilimumab in combination will provide a first-line treatment for patients with previously untreated advanced or metastatic gastric or gastroesophageal junction cancer.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate649;** NCT02872116; 2016-001018-76; A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab Plus Ipilimumab or Nivolumab in Combination With Oxaliplatin Plus Fluoropyrimidine Versus Oxaliplatin Plus Fluoropyrimidine in Subjects With Previously Untreated

	Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer **Phase III –** active, not recruiting **Location(s): EU (incl UK), USA, Canada and other countries** **Primary Completion Date: May 2020**
Trial design	Randomized, parallel assignment, open label
Population	N=2031; 18+ only; Must have gastric cancer or gastroesophageal junction cancer that cannot be operated on and that is advanced or has spread out; Did not receive neoadjuvant or adjuvant treatment (chemotherapy, radiotherapy, or both) for their disease within the last 6 months
Intervention(s)	• Nivolumab + Ipilimumab • Nivolumab + Oxaliplatin + Capecitabine • Ipilimumab + Oxaliplatin + Leucovorin + Fluorouracil
Comparator(s)	• Oxaliplatin + Capecitabine (XELOX) • Oxaliplatin + Leucovorin + Fluorouracil (FOLFOX)
Outcome(s)	• Overall survival (OS) of nivolumab in combination with oxaliplatin + fluoropyrimidine versus oxaliplatin + fluoropyrimidine in programmed cell death ligand 1 (PD-L1) positive participants [time frame: up to 53 months after the first participant is randomised] • Progression-free survival (PFS), as assessed by Blinded Independent Central Review (BICR), of nivolumab in combination with oxaliplatin + fluoropyrimidine versus oxaliplatin + fluoropyrimidine in PD-L1 positive participants [time frame: up to 53 months after the first participant is randomised] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Nivolumab (Opdivo) is already marketed in the UK. The NHS indicative prices for nivolumab solution for infusion vials are as follows:[22]

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

Ipilimumab (Yervoy) is already marketed in the UK. The NHS indicative prices for ipilimumab solution for infusion vials are as follows:[23]

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

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

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab for gastric or gastroesophageal junction adenocarcinoma (ID1305). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab in combination with chemotherapy for untreated advanced gastric cancer [ID1465]. Expected publication date: October 2021
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010.
- NICE 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 submucosal dissection of gastric lesions (IPG360). October 2010.
- NICE interventional procedure guidance. Laparoscopic gastrectomy for cancer (IPG269). July 2008.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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.
- NHS England. Clinical Commissioning Policy: Robotic assisted surgery for oesophago-gastric cancers. 16006/P. July 2016

OTHER GUIDANCE

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- London Cancer Alliance (LCA). LCA Oesophageal and Gastric Cancer Clinical Guidelines. 2014.[26]
- Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. 2011.[27]

ADDITIONAL INFORMATION

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