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# Nivolumab in addition to chemotherapy for advanced gastric cancer – first line

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## LAY SUMMARY

Gastric cancer is cancer that starts anywhere inside the stomach or the stomach wall. Advanced gastric cancer can be locally advanced (has spread into the tissues around the stomach) or metastatic (has spread to at least one other part of the body such as the liver). Most gastric cancer cases are diagnosed at a late stage. Advanced cancers have poor prognosis and usually cannot be cured. However, it may be controlled, and symptoms can be relieved through treatment.

Nivolumab is a medicinal product that is currently licensed in the UK for the treatment of several types of advanced cancers such as melanoma, non-small cell lung cancer, and kidney cancer. It is a monoclonal antibody that acts by preventing the inhibition of T-cells (part of the body's immune system that fight cancer) through binding to a protein called programmed cell death 1 (PD-1). Nivolumab is being developed to be used in addition to chemotherapy for the treatment of patients with advanced gastric cancer who have not had treatment previously. If licensed, nivolumab in combination with chemotherapy will offer an additional first-line treatment option for this patient group.



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## TARGET GROUP

Gastric cancer (advanced) – first line; in combination with chemotherapy

## TECHNOLOGY

### DESCRIPTION

Nivolumab (Opdivo®) is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death 1 (PD-1) receptor and selectively blocks interaction with its programmed death ligands PD-L1 and PD-L2. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumour tissue. The inhibitory effect of PD-1 and its ligands occurs through the promotion of apoptosis in antigen specific T cells while simultaneously blocking apoptosis in suppressor T cells. Blocking PD-1 activity has been shown to lead to decreased tumour growth in mouse tumour models.[1]

In the phase III clinical trial (NCT02872116; CheckMate649), nivolumab 10 mg/ml solution for injection/infusion is given in addition to chemotherapy (XELOX (Oxaliplatin + Capecitabine) or FOLFOX (Oxaliplatin + Leucovorin + Fluorouracil)) in two of the five arms of the study. No further details regarding treatment regimen (treatment duration, follow-up) are reported.[2,3]

Nivolumab as monotherapy is currently licensed in the UK for:[4]

- Treatment of unresectable or metastatic advanced melanoma
- Treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy
- Treatment of advanced renal cell carcinoma after prior therapy
- Treatment of locally advanced unresectable or metastatic urothelial carcinoma, after failure of prior platinum-containing therapy
- Treatment of squamous cell cancer of the head and neck, progressing on or after platinum-based therapy
- Treatment of relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin

Common or very common adverse effects of nivolumab are abdominal pain; alopecia; arthralgia; blurred vision; colitis; constipation; cough; decreased appetite; diarrhoea; dizziness; dry eyes; dry mouth; dry skin; dyspnoea; erythema; headache; hyperglycaemia; hypertension; infusion-related reactions; malaise; musculoskeletal pain; nausea; oedema; peripheral neuropathy; pneumonitis; pruritus; pyrexia; rash; stomatitis; thyroid disorders; upper respiratory tract infection; vitiligo; vomiting.[4] For further details see the Summary of Product Characteristics (SmPC).[5]

Nivolumab monotherapy and in combination with other therapies is currently in phase III stage of development for a range of different types of cancers.[6]

## INNOVATION and/or ADVANTAGES

A phase III clinical trial in Asia (NCT02267343) investigated the safety and efficacy of nivolumab in patients with gastric cancer or gastroesophageal junction cancer that were refractory to or intolerant of standard therapy.[7,8] This trial suggests a rationale to support the investigation of nivolumab plus chemotherapy in earlier lines of treatment with potential survival benefits.[9,8] If licensed, nivolumab in

combination with chemotherapy will offer an additional first-line treatment option for patients with advances gastric cancer.

## DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd

## REGULATORY INFORMATION/ MARKETING PLANS

Nivolumab is a designated orphan drug in the USA for the treatment of gastric cancer and gastro-oesophageal junction cancer (December 2016).[10]

## PATIENT GROUP

## BACKGROUND

Gastric cancer is cancer of the stomach. Gastric cancer can start anywhere inside the stomach or within the stomach wall. Most gastric cancers start in the gland cells (cells that make mucus) in the inner stomach lining.[11]

Advanced gastric cancer is cancer that began in the stomach and has spread into the tissues around the stomach (locally advanced) or spread to at least one other part of the body (metastatic), such as the liver, lungs, lymph nodes, or the oesophagus. Advanced cancer cannot usually be cured, but treatment may control it, relieve the symptoms, and give the patient a good quality of life.[12]

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, producing a lump of tissue called tumour. It is not known what triggers the changes in DNA that lead to gastric cancer. Some factors increase the risk of gastric cancer such as aging (55 years and older), male gender, smoking, severe chronic atrophic gastritis (long term inflammation of the stomach lining) and peptic ulcer caused by *Helicobacter pylori* infection, diet such as pickled vegetables, salt, and smoked meat), family history of gastric cancer, having another type of cancer, vitamin B12 deficiency, and history of stomach surgery.[14]

Common symptoms of gastric cancer include blood in stools or black stools, loss of appetite, weight loss, sickness, tiredness, breathlessness, lumpiness and swelling in the stomach (caused by a build-up of fluid), abdominal pain, persistent indigestion (dyspepsia) and burping, anaemia, and jaundice.[13, 14]

Late complications of gastric cancer may include pathologic peritoneal and pleural effusions, obstruction of the gastric outlet or gastroesophageal junction, obstruction of the small bowel, bleeding in the stomach from oesophageal varices (abnormal large veins in the oesophagus) or at the anastomosis after surgery, jaundice caused by hepatomegaly, weakness and weight loss from not eating.[15] The prognosis of patients with unresectable or metastatic gastric cancer is poor and the median survival time ranges between 6 and 12 months.[16]

## CLINICAL NEED and BURDEN OF DISEASE

In 2014, gastric cancer was the 17th most common cancer in the UK. There were around 6,900 new cases of stomach cancer in the UK in 2013-2015, equivalent to 19 cases diagnosed every day.[17] The crude incidence rate in England was 10.0 per 100,000 in 2015. Between 2013 and 2015 around half (51%) of stomach cancer cases in the UK each year were diagnosed in people aged 75 years and over. The proportion of gastric cancer cases in England diagnosed at stage III and stage IV in 2014 were 17%

and 34% respectively. According to 2010-2012 data in the UK, the largest proportion of gastric cancer cases (34.0% males, 19.7% females) occur in the cardia[18] (The first part of the stomach which is closest to the oesophagus[19]).

Hospital episode statistics for England 2016/17 show that there were 20,249 hospital admissions for malignant neoplasm of stomach (ICD 10: C16), with 25,605 finished consultant episodes (FCE) resulting in 62,477 FCE bed days.[20]

According to 2010-2011 data, 19% of people diagnosed with stomach cancer in England and Wales survive their disease for five years or more.[17] Five year survival rates for stage III (A, B, C) gastric cancer were 25%, 20%, and 10% respectively; whereas those for stage IV was 5%.[21]

Gastric cancer was the 12th most common cause of cancer death in the UK in 2014. Crude mortality rate in England was 6.7 per 100,000 in 2014. In the UK, it is the eighth most common cause of cancer death in males, whilst it is the 13th most common cause of cancer death in females. Gastric cancer mortality is strongly related to age, with the highest mortality rates being in older males and females. In the UK in 2012-2014, on average each year around 6 in 10 (59%) deaths were in people aged 75 and over.[22]

## PATIENT PATHWAY

## 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. Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer (ID1096). Expected date of issue to be confirmed.
- NICE technology appraisal. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (TA208). November 2010.
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010.
- NICE guideline in development. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.
- NICE quality standard in development. Oesophago-gastric cancer (GID-QS10062). Expected 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.
- NICE interventional procedure guidance. Laparo-endogastric surgery (IPG25). December 2003.

### NHS ENGLAND and POLICY 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

- Gastric Cancer, Version 3. 2016, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2016; 14:1286-1312.[23]
- Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 27 (Supplement 5): v38–v49, 2016.[24]
- LCA Oesophageal and Gastric Cancer Clinical Guidelines. April 2014.[25]
- Guidelines for the management of oesophageal and gastric cancer. Gut 2011; 60: 1449e1472.[26]

## CURRENT TREATMENT OPTIONS

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.[27, 28]

Chemotherapy is a specialist treatment for cancer that uses medicines, called cytotoxic medicines, to stop cancer cells dividing and multiplying. 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.[27] The followings are recommendations by the National Institute for Health and Care Excellence (NICE) as first-line palliative chemotherapy for locally advanced or metastatic oesophageal or gastric cancer:[29]

- **Trastuzumab**

Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:

- have not received prior treatment for their metastatic disease and
- have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).

People who are currently receiving treatment with trastuzumab for HER2-positive metastatic gastric cancer who do not meet the criteria above should have the option to continue treatment until they and their clinicians consider it appropriate to stop.[30]

- **Capecitabine**

Capecitabine in combination with a platinum-based regimen for the first-line treatment of inoperable advanced gastric cancer. [31]

## EFFICACY and SAFETY

| | |
|---|---|
| **Trial** | **CheckMate649, NCT02872116, EudraCT Number: 2016-001018-76; Nivolumab + Ipilimumab vs Nivolumab + XELOX (Oxaliplatin + Capecitabine) vs Nivolumab + FOLFOX (Oxaliplatin + Leucovorin + Fluorouracil) vs XELOX vs FOLFOX ; phase III** |
| **Sponsor** | Bristol-Myers Squibb |
| **Status** | Ongoing |
| **Source of Information** | Trial registry.[2,3] |
| **Location** | EU (incl UK), USA, Canada and other countries. |
| **Design** | Randomised, active-controlled, multicentre, open-label. |
| **Participants** | n= 1266 (planned); aged 18 and older; males or females; gastric cancer or gastroesophageal junction cancer; cannot be operated on; advanced or metastatic; did not receive neoadjuvant or adjuvant treatment (chemotherapy, radiotherapy, or both) for their disease within the last 6 months. |
| **Schedule** | The following interventions are administered in this clinical trial:<br>Nivolumab 10 milligram(s)/millilitre (mg/ml) intravenous (IV); Ipilimumab 5 mg/ml IV; Oxaliplatin 5mg/ml IV; Capecitabine 150 mg or 500mg orally; Leucovorin (Folinic Acid) 50 mg/ml IV; Fluorouracil 50 mg/ml IV<br>Participants are randomised to:<br>• Nivolumab + Ipilimumab for 4 doses, followed by Nivolumab monotherapy<br>• XELOX (Oxaliplatin + Capecitabine)<br>• FOLFOX (Oxaliplatin + Leucovorin + Fluorouracil)<br>• Nivolumab + XELOX<br>• Nivolumab + FOLFOX |
| **Follow-up** | Active treatment period not reported, follow-up 40 months. |
| **Primary Outcomes** | • Overall survival (OS) [time point: 40 months after first patient is randomised]<br>• Progression-free Survival (PFS) as assessed by BICR [time point: 27 months after first patient is randomised]<br>• Objective Response Rate (ORR) as assessed by BICR [time point: 20 months after first patient is randomised] |
| **Secondary Outcomes** | • OS [time point: 40 months after first patient is randomised]<br>• PFS assessed by BICR [time point: 27 months after first patient is randomised]<br>• Time to Symptom Deterioration (TTSD) [time point: 40 months after first patient is randomised]<br>• ORR by investigator [time point: 20 months after first patient is randomised]<br>• PFS by investigator] |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |
| **Expected reporting date** | Study completion date reported as October 2021. |

## ESTIMATED COST and IMPACT

### COST

Nivolumab is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[4]

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

### IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ 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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