

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma**Final scope****Remit/appraisal objective**

To appraise the clinical and cost effectiveness of nivolumab in combination with chemotherapy within its marketing authorisation for untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

Background

Gastric cancer is a malignant tumour arising from cells in the stomach. The most common type of stomach cancer is gastric or gastro-oesophageal junction¹. Gastro-oesophageal junction cancer describes cancers where the centre of the tumour is less than 5cm above or below where the oesophagus meets the stomach¹. Oesophageal cancer is a malignant tumour arising from cells lining the oesophagus. The most common histological subtype of gastric, gastro-oesophageal junction and oesophageal cancer is adenocarcinoma^{2,3}.

Stomach cancer is more common in men than women, with approximately 3,378 cases diagnosed in men, and 1,764 cases in women in England in 2017⁴. Around half of all new cases of gastric cancer in the UK are diagnosed in people aged 75 years and over⁴. Oesophageal cancer is also more common in men than women, with approximately 5,280 cases diagnosed in men, and 2,289 cases in women in England in 2017⁵. Around 41% of all new cases of oesophageal cancer in the UK are diagnosed in people aged 75 and over⁵.

Initial symptoms of gastric or oesophageal cancer are vague and are similar to other stomach conditions, but symptoms of advanced stages may include a lack of appetite and subsequent weight loss; fluid in the abdomen, vomiting blood, blood in the stool or black stool. Because of the nature of symptoms, gastric and oesophageal cancer are often diagnosed at an advanced stage, with around 17% and 29% diagnosed at stage 3 (locally advanced), and 34% and 30% diagnosed at stage 4 (metastatic) for gastric and oesophageal cancer respectively in England in 2014^{4,5}. The 5-year survival for people diagnosed with stomach cancer and oesophageal cancer between 2013 and 2017 was 21.6% and 17% respectively⁶.

Over the past few years there has been a rapid increase in incidence of tumours at the junction of the oesophagus and stomach. These tend to come from changes in the lining of the oesophagus, in turn leading to adenocarcinoma of the lowest part of the oesophagus, which goes across the gastroesophageal junction.

The aim of treatment in advanced or metastatic gastric, gastro-oesophageal junction cancer or oesophageal adenocarcinoma is primarily palliative; to prevent progression, extend survival and relieve symptoms with minimal adverse effects. NICE technology appraisal 191 recommends capecitabine in combination with a platinum-containing agent as an option for inoperable untreated advanced gastric cancer. NICE clinical guideline (NG 83) recommends chemotherapy combination regimens for people who have a performance status 0 to 2 and no significant comorbidities. Chemotherapy regimens include doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin or triplet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin. For people who have untreated HER2-positive metastatic gastric or gastro-oesophageal junction adenocarcinoma, NICE technology appraisal 208 recommends trastuzumab in combination with cisplatin and capecitabine or fluorouracil.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a humanised monoclonal antibody that targets and blocks a receptor on the surface of lymphocytes known as PD-1. This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. It is administered intravenously.

Nivolumab in combination with chemotherapy does not have a marketing authorisation in the UK for locally advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. It is being studied in a clinical trial which randomised patients into three treatment arms; nivolumab in combination with chemotherapy, nivolumab in combination with ipilimumab and chemotherapy only. The trial enrolled adults with untreated locally advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

Intervention	Nivolumab in combination with chemotherapy
Population	Adults with untreated locally advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

Comparators	<ul style="list-style-type: none"> • Chemotherapy without nivolumab, such as: <ul style="list-style-type: none"> ○ Doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin ○ Triplet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin plus epirubicin • For people with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma <ul style="list-style-type: none"> ○ Trastuzumab with cisplatin plus capecitabine or fluorouracil
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.</p>
Other considerations	<p>If evidence allows subgroups by PD-L1 status will be considered.</p> <p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
Related NICE recommendations	<p><u>Related Technology Appraisals:</u></p> <p>‘Capecitabine for the treatment of advanced gastric</p>

and NICE Pathways	<p>cancer' (2010). NICE technology appraisal 191. Static list</p> <p>Trastuzumab for the treatment of HER2-positive metastatic gastric cancer' (2010) NICE technology appraisal 208. Static list.</p> <p>Appraisals in development:</p> <p>Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer' NICE technology appraisals guidance [ID1096] Publication date to be confirmed.</p> <p>Pembrolizumab for untreated metastatic gastric or gastro-oesophageal junction cancer' NICE technology appraisals guidance [ID1305] Publication date to be confirmed.</p> <p>Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer' NICE technology appraisals guidance [ID3742] Publication date to be confirmed</p> <p>Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer' NICE technology appraisals guidance [ID3741] Publication date to be confirmed.</p> <p>Nivolumab with platinum-based chemotherapy for advanced unresectable, recurrent or metastatic previously untreated oesophageal cancer' NICE technology appraisals guidance [ID2712] Publication date to be confirmed</p> <p>Related Guidelines:</p> <p>Oesophago-gastric cancer: assessment and management in adults' (2018). NICE guideline 83 Review date January 2020.</p> <p>Related Interventional Procedures:</p> <p>Laparoscopic gastrectomy for cancer' (2008). NICE interventional procedures guidance 269.</p> <p>Related Quality Standards:</p> <p>Oesophago-gastric cancer (2018) NICE quality standard 176.</p> <p>Related NICE Pathways:</p> <p>Gastrointestinal cancers (2016) NICE Pathway</p>
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	Oesophageal and gastric cancer (2020) NICE Pathway
Related National Policy	<p>The NHS Long Term Plan, 2019. NHS Long Term Plan</p> <p>NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View'</p> <p>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 105, Specialist Cancer services (adults)</p> <p>Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domain 1.</p>

References

1. Cancer Research UK. [About gastro oesophageal junction cancer](#). 2018. Accessed November 2020
2. Macmillan Cancer Support [Types of stomach cancer](#). Accessed November 2020.
3. Cancer research UK [Oesophageal cancer types](#) Accessed November 2020
4. Cancer Research UK [Stomach cancer incidence statistics](#). Accessed November 2020.
5. Cancer Research UK. [Oesophageal Cancer Incidence Statistics](#). 2017. Accessed November 2020
6. Office for National Statistics (2019). [Cancer survival in England - adults diagnosed](#). Accessed November 2020.