NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer [ID3742]

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of pembrolizumab with trastuzumab and chemotherapy within its marketing authorisation for treating untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer.

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 junction[1]. Gastro-oesophageal junction cancer describes cancers where the centre of the tumour is less than 5cm above or below where the oesophagus meets the stomach[1]. 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 2017[4]. Around half of all new cases of gastric cancer in the UK are diagnosed in people aged 75 years and over[4]. 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 2017[5]. Around 41% of all new cases of oesophageal cancer in the UK are diagnosed in people aged 75 and over[5].

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% respectively[6].

Over the past few years there has been an 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 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, that express high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive), NICE technology appraisal 208 recommends trastuzumab in combination with cisplatin and capecitabine or fluorouracil.

The technology

Pembrolizumab (Keytruda, MSD) with trastuzumab and chemotherapy does not currently have a marketing authorisation in the UK for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer. It is currently being studied in clinical trials in people with previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction cancer.

Pembrolizumab as a monotherapy or in combination with various medicinal products is currently licensed in the UK for the following related indications:

- Locally advanced unresectable or metastatic oesophageal carcinoma
- HER2-negative gastro-oesophageal junction adenocarcinoma (tumours express PD-L1 with combined positive score of 10 or more)
- Cancers described as microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) located in gastric cancer, small intestine cancer, biliary cancer

Intervention(s)	Pembrolizumab with trastuzumab and chemotherapy
Population(s)	People with untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer
Subgroups	If the evidence allows, the following subgroups will be considered: • HER2 status by IHC score

Comparators	• Chemotherapy only, which includes:
	  ○ doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin
	  ○ triplet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin
	• Trastuzumab with cisplatin plus capecitabine or fluorouracil

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	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.
Related NICE recommendations	**Related Technology Appraisals:** 'Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer' NICE technology appraisals guidance 737. 'Capecitabine for the treatment of advanced gastric cancer' (2010). NICE technology appraisal 191. Static list 'Trastuzumab for the treatment of HER2-positive metastatic gastric cancer' (2010) NICE technology appraisal 208. Static list. **Related appraisals in development:** 'Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma' NICE technology appraisals guidance [ID1465] Publication expected September 2022. 'Pembrolizumab with chemotherapy and surgery for treating resectable gastric or gastro-oesophageal junction cancer'

	NICE technology appraisals guidance [ID2696] Publication date to be confirmed. 'Pembrolizumab for untreated metastatic gastric or gastro-oesophageal junction cancer' NICE technology appraisals guidance [ID1305] Publication date to be confirmed. 'Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer' NICE technology appraisals guidance [ID3741] Publication date to be confirmed. '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 **Related Guidelines:** 'Oesophago-gastric cancer: assessment and management in adults' (2018). NICE guideline 83. Last reviewed August 2022. **Related Interventional Procedures:** 'Laparoscopic gastrectomy for cancer' (2008). NICE interventional procedures guidance 269. **Related Quality Standards:** Oesophago-gastric cancer (2018) NICE quality standard 176.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019)

Questions for consultation

Where do you consider pembrolizumab with trastuzumab and chemotherapy will fit into the existing care pathway for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer?

Should any other subgroups be considered e.g. people with tumours expressing PD-L1?

Would pembrolizumab with trastuzumab and chemotherapy be a candidate for managed access?

Do you consider that the use of pembrolizumab with trastuzumab and chemotherapy can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab with trastuzumab and chemotherapy will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

1. Cancer Research UK. About gastro oesophageal junction cancer. 2022. Accessed September 2022.

2. Macmillan Cancer Support. Types of stomach cancer. Accessed September 2022.

3. Cancer Research UK. Oesophageal cancer types. Accessed September 2022.

4. Cancer Research UK. Stomach cancer incidence statistics. Accessed September 2022.

5. Cancer Research UK. Oesophageal cancer incidence statistics. 2017. Accessed September 2022.

6. Office for National Statistics (2019). Cancer survival in England - adults diagnosed. Accessed September 2022.