NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab in combination with ipilimumab for untreated advanced unresectable recurrent or metastatic oesophageal cancer Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab in combination with ipilimumab within its marketing authorisation for untreated advanced unresectable recurrent or metastatic oesophageal cancer.

Background

Oesophageal cancer is a malignant tumour arising from cells lining the oesophagus (gullet), which is the muscular tube through which food passes from the throat to the stomach. The two main types of oesophageal cancer are squamous cell carcinoma and adenocarcinoma. In the upper and middle part of the oesophagus, cancers tend to be squamous cell carcinomas, which develop from cells that make up the inner lining of the oesophagus. Cancers in the lower part tend to adenocarcinomas, which usually develop in gland cells.[1] When the tumour includes both cancer types it is called adenosquamous carcinoma. Adenosquamous carcinoma is a rare type of oesophageal cancer. The most common symptoms are difficulty swallowing, food regurgitation, nausea or vomiting, unexplained weight loss and persistent indigestion or cough.[2]

Oesophageal cancer is more common in men than women. In 2017, there were 2,289 new diagnoses in women and 5,280 in men (a total of 7,569 new cases) in England.[3] The risk of developing oesophageal cancer increases with age. Around 40% of all new cases in UK are diagnosed in people aged over 75.[4] Because of the nature of symptoms, oesophageal cancer is often diagnosed at an advanced stage. On average 70-80% are diagnosed at stage 3 (locally advanced) or 4 (metastatic).[5] For adults diagnosed between 2013 and 2017 in England, the 1-year survival rate for people with oesophageal cancer is around 47% and 5-year survival rate is 17%.[6]

The aim of treatment in advanced or metastatic oesophageal cancer is primarily palliative. NICE clinical guideline (NG83) 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.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a fully humanised IgG4 monoclonal antibody which targets the programmed cell death-1 receptor (PD-1), to promote an anti-tumour immune response. It is administered intravenously.

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a recombinant human anti-CTLA-4 monoclonal antibody which blocks the effects of CTLA-4 to enhance T-cell mediated immune responses to tumour cells.

Nivolumab in combination with ipilimumab does not currently have a marketing authorisation for oesophageal cancer in the UK. It has been studied in a randomised clinical trial, compared with nivolumab in combination with fluorouracil plus cisplatin, and with fluorouracil plus cisplatin in people with advanced unresectable, recurrent or metastatic previously untreated oesophageal cancer (squamous cell carcinoma or adenosquamous cell carcinoma of oesophagus).

Nivolumab in combination with fluorouracil plus cisplatin is subject to an ongoing appraisal (ID2712). A consultation on the suggested remit, draft scope and provisional stakeholder list of consultees and commentators for this topic was carried out between September and October 2020.

Intervention(s)	Nivolumab in combination with ipilimumab
Population(s)	People with untreated advanced unresectable, recurrent or metastatic oesophageal squamous cell carcinoma

Comparators	• Platinum-based chemotherapy without nivolumab, such as:
	  ○ doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin
	  ○ triplet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin plus epirubicin
	• Pembrolizumab with platinum-based chemotherapy (subject to ongoing appraisal [ID3741])
	• Nivolumab in combination with cisplatin plus fluorouracil(subject to ongoing appraisal [ID2712])

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 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	If the evidence allows subgroups by degree of PD-L1 expression and cancer histology will be considered. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. 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 and NICE Pathways	**Related Technology Appraisals:** None **Appraisals in development:** Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer ID3742 NICE technology appraisal guidance. Publication date to be confirmed. Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal or gastroesophageal junction cancer [ID3741] NICE technology appraisal guidance. Publication date October 2021. Nivolumab with platinum-based chemotherapy for advanced unresectable, recurrent or metastatic previously untreated oesophageal cancer [ID2712] NICE technology appraisal guidance. Publication date to be confirmed. **Related Guidelines:** Oesophago-gastric cancer: assessment and management in adults (2018) NICE guideline NG83. Review date: not published.

	Related Interventional procedures: Minimally invasive oesophagectomy (2011) NICE interventional procedures guidance 407 Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia (2010) NICE interventional procedures guidance 355 Palliative photodynamic therapy for advanced oesophageal cancer (2007) NICE interventional procedures guidance 206 **Related Quality Standards:** Oesophago-gastric cancer (2018) NICE quality standard 176 Related NICE Pathways: Oesophageal and gastric cancer overview (2020), NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018) Manual for Prescribed Specialised Services 2018/19. Chapter 105, Specialist Cancer services (adults) Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017. Domains 1 and 2.

Questions for consultation

Would it be appropriate to assess nivolumab in combination with ipilimumab and nivolumab in combination with cisplatin plus fluorouracil (ID2712) in the same technology appraisal; that is, as a multiple technology appraisal (MTA)?

Have all relevant comparators for nivolumab in combination with ipilimumab been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for advanced unresectable, recurrent or metastatic oesophageal cancer that has not been previously treated?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom nivolumab in combination with ipilimumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

- If evidence allows, should squamous cell carcinoma and adenosquamous cell carcinoma be considered separately?

Where do you consider nivolumab in combination with ipilimumab will fit into the existing NICE pathway, Oesophageal and gastric cancer overview?

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 the treatment will be licenced.

- 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.

Do you consider nivolumab in combination with ipilimumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of nivolumab in combination with ipilimumab can result in any potential significant and 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 Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Macmillan cancer support (2020) Signs and symptoms of oesophageal cancer. Accessed April 2020

2. Macmillan cancer support (2020) What is oesophageal cancer? Accessed April 2020.

3. Office for National Statistics (2019) Cancer registration statistics, England, 2017. Accessed March 2020.

4. Cancer Research UK (2019) Oesophageal cancer incidence statistics. Accessed March 2020.

5. NCRAS (2019). Stage breakdown by CCG 2017. Accessed March 2020.

6. Office for National Statistics (2019) Cancer survival in England - adults diagnosed Accessed March 2020.