NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with platinum-based chemotherapy or ipilimumab for untreated advanced, unresectable or recurrent or squamous cell oesophageal cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy, or ipilimumab within their marketing authorisations for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma.

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. NICE technology appraisal 737 recommends pembrolizumab with platinum- and fluoropyrimidine-based as an option for untreated locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 10 or more.

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 fluoropyrimidine- and platinum-based combination chemotherapy or ipilimumab does not currently have a marketing authorisation for oesophageal cancer in the UK. Nivolumab combined with fluorouracil plus cisplatin and nivolumab and ipilimumab have been studied in a randomised clinical trial, compared with fluorouracil plus cisplatin in people with advanced unresectable, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma.

Intervention(s)	Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy, and 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
	For tumours that express PD-L1 with a combined positive score (CPS) of 10 or more:
	• Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy

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:** Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (2021] NICE technology appraisal guidance 737. Review date 2024. **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. **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 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.

References

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