# Health Technology Briefing
# August 2024

# Durvalumab with chemoradiation for untreated locally advanced unresectable oesophageal squamous cell carcinoma

| Company/Developer | AstraZeneca UK Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 33917 | NICE ID: Not available | UKPS ID: 670185 |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials

## Summary

Durvalumab in combination with definitive chemoradiation is in clinical development for the treatment of locally advanced, unresectable oesophageal squamous cell carcinoma. This is a type of cancer that begins in the thin, flat cells lining the food pipe (oesophagus), that has spread into surrounding tissues in the oesophagus, and is untreatable by surgery. Symptoms include difficulty swallowing, persistent indigestion or heartburn, weight loss, pain in the throat, and chronic cough. In the UK, oesophageal carcinoma is more common in older people (≥75 years old) and males. There is a need for new treatment options, as most patients experience disease progression within two years of being treated with the current standard of care.

Durvalumab is administered as an infusion intravenously. It is a monoclonal antibody, a type of protein designed to attach to a protein called programmed cell death ligand-1 (PD-L1), which is present on the surface of many cancer cells. PD-L1 acts to switch off immune cells that would otherwise attack the cancer cells. By attaching to PD-L1 and blocking its effects, durvalumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease. If licensed, durvalumab will offer an additional treatment option for patients with locally advanced, unresectable oesophageal squamous cell carcinoma.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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## Proposed Indication

Treatment of locally advanced, unresectable, oesophageal squamous cell carcinoma (SCC) in adults during definitive chemoradiotherapy (dCRT).[1]

## Technology

### Description

Durvalumab (Imfinzi) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) with programmed cell death protein 1 (PD-1) and CD80 (B7.1). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interaction enhances antitumour immune responses and increases T-cell activation. Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system.[2] By attaching to PD-L1 and blocking its effects, durvalumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease.[3]

Durvalumab in combination with dCRT is in clinical development for treatment of locally advanced, unresectable oesophageal SCC. In the phase III clinical trial (KUNLUN, NCT04550260), patients receive durvalumab as an intravenous infusion in addition to radiation combined with cisplatin and fluorouracil or combined with cisplatin and capecitabine.[1]

### Key Innovation

For patients with locally advanced, unresectable oesophageal SCC, definitive chemoradiotherapy (dCRT) is the current standard of care; however, up to half of patients will experience disease progression within two years of dCRT, and overall survival rates remain suboptimal. The combination of immune checkpoint inhibitors with chemoradiotherapy has demonstrated synergistic antitumour activity in pre-clinical models, and recent clinical data has demonstrated clinical benefit of combined PD-L1 inhibition and preoperative chemoradiotherapy (CRT) in patients with locally advanced oesophageal SCC.[4]

If licensed, durvalumab will offer an additional treatment option for untreated patients with locally advanced, unresectable, oesophageal squamous cell carcinoma.

### Regulatory & Development Status

Durvalumab is licensed in the EU/UK for the following indications:[2]

- non-small cell lung cancer
- small cell lung cancer
- biliary tract cancer
- hepatocellular carcinoma

Durvalumab as a monotherapy or in combination with other medicinal products is in phase II and phase III clinical development for indications including but not limited to, biliary tract neoplasms, solid tumours and haematological malignancies.[5]

## Patient Group

### Disease Area and Clinical Need

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Oesophageal cancer is cancer that is found anywhere within the oesophagus, which connects the mouth to the stomach.[6] There are two main types of oesophageal cancer: SCC and adenocarcinoma. SCC is less common than adenocarcinoma in the UK. Cancers in the upper or middle oesophagus are usually SCC.[7,8] Locally advanced cancer means that the cancer has spread into the tissues around the oesophagus and has not spread to other organs in the body.[9] Locally advanced or metastatic cancers that cannot be removed with surgery are referred to as unresectable.[10] The most common symptoms of oesophageal cancer include: difficulty swallowing, persistent indigestion or heartburn, unexplained weight loss and pain in the throat or behind the breastbone.[11] Some of the risk factors for oesophageal cancer are age; with 41% of new cases in people over 75 years of age, being overweight/obese, smoking or using tobacco, drinking alcohol, having Barrett's oesophagus, having gastro-oesophageal reflux disease, having radiotherapy and drinking very hot drinks.[12,13]

Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-18).[13] The age standardised incidence rate of malignant neoplasm of the oesophageal in England (2017) is 22.2 and 8.1 per 100,000 amongst males and females respectively.[14] In England (2022-23), there were 45,092 finished consultant episodes (FCE) and 36,834 admissions for malignant neoplasms of the oesophagus (ICD-10 code C15) which resulted in 83,355 FCE bed days and 29,550 day cases.[15] In England (2017), there were 7,569 patients diagnosed with oesophageal cancer and 6,458 deaths registered where neoplasms of the oesophagus was the underlying cause.[14] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year standardised survival rates were 46.5% and 17.0% respectively.[16]

## Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following:

- Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.[17]
- Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer.[18]

## Clinical Trial Information

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| Trial | **KUNLUN, NCT04550260, EudraCT2020-001001-22;** A Phase III, Randomized, Double-Blind, Placebo Controlled, Multi-Center, International Study of Durvalumab Given Concurrently With Definitive Chemoradiation Therapy in Patients With Locally Advanced, Unresectable Esophageal Squamous Cell Carcinoma (KUNLUN)<br>**Phase III**- Active, not recruiting<br>**Locations:** 4 EU countries, USA, Canada, and other countries<br>**Primary completion date:** November 2025 |
| Trial Design | Randomised, parallel assignment, quadruple blind |
| Population | N=640 (estimated); patients with histologically or cytologically confirmed oesophageal squamous cell carcinoma, and present with locally advanced, unresectable disease (Stage II-IVA) |
| Intervention(s) | • Durvalumab (intravenous, IV)<br>• Cisplatin+ Fluorouracil |

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| | • Cisplatin+ Capecitabine<br>• Radiation |
| Comparator(s) | • Durvalumab matching placebo (IV)<br>• Cisplatin+ Fluorouracil<br>• Cisplatin+ Capecitabine<br>• Radiation |
| Outcome(s) | **Primary outcome measure:**<br>Progression free survival (PFS) per response evaluation criteria in solid tumours (RECIST) 1.1 as assessed by blinded, independent, central review (BICR) [Time Frame: up to approximately 56 months]<br><br>See trial record for full list of all outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

Durvalumab is already marketed in the UK; a 120mg/2.4mls concentrate for solution for infusion costs £592 per vial, and £2,466 for 500mg/10mls per vial.[19]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Toripalimab with chemotherapy for treating advanced oesophageal squamous cell cancer without previous systemic chemotherapy (ID6414). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated unresectable metastatic oesophageal squamous cell carcinoma (ID1629). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tislelizumab with chemotherapy for untreated advanced oesophageal squamous cell cancer (ID5113). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with chemoradiotherapy for untreated unresectable oesophageal cancer. (ID11852). Expected date of issue to be confirmed.
- NICE technology appraisal. Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma. (TA865). Published February 2023.
- NICE technology appraisal. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer. (TA737). Published October 2021.
- NICE clinical guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.
- NICE quality standard. Oesophago-gastric cancer (QS176). December 2018.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy Proposition: 18F-flourodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) as part of radical radiotherapy treatment planning for oesophageal cancer (all ages). Publishing date to be confirmed.

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- 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.

### Other Guidance

- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. 2019.[20]
- European Society for Medical Oncology (ESMO). ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up: Oesophageal cancer. 2016.[21]
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology, and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. 2011.[22]

## Additional Information

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