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Newcastle University

# Health Technology Briefing
# September 2023

# Durvalumab with fluorouracil, leucovorin, oxaliplatin and docetaxel chemotherapy for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer

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

| NIHRIO ID: 33898 | NICE TSID: Not Available | UKPS ID: 670186 |
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## Licensing and Market Availability Plans

Currently in phase III clinical development.

## Summary

Durvalumab in combination with chemotherapy is in clinical development for the treatment of resectable gastric cancer and gastro-oesophageal junction (GEJ) adenocarcinoma. Gastric cancers and GEJ adenocarcinoma are cancers that form in the inner lining of the stomach or where the stomach and the oesophagus meet. Risk factors of these cancers include obesity, older age, gastro-oesophageal reflux disease and long-term helicobacter pylori infection. Symptoms can include difficulty and pain when swallowing, nausea or vomiting, heartburn, indigestion, loss of appetite, fatigue, unexplained weight loss, or a lump in the upper abdomen. There is an unmet need to improve survival outcomes, as many patients who have been treated with surgery and chemotherapy often experience disease recurrence.

Durvalumab is a monoclonal antibody (a type of protein) which is administered by intravenous infusion. It attaches 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 and kill 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, thereby slowing disease progression. In clinical trials, durvalumab with chemotherapy before (neoadjuvant) and after (adjuvant) surgery has shown clinical improvement in the disease. If licensed, durvalumab in combination with chemotherapy will provide an additional neoadjuvant and adjuvant treatment option for patients with resectable gastric cancer or GEJ adenocarcinoma.

## Proposed Indication

For the neoadjuvant and adjuvant treatment of resectable gastric or gastro-oesophageal junction (GEJ) adenocarcinoma in patients aged 18 years and older.[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 PD-1 and CD80. Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection by the immune system. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80. By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. The selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation.[2]

Durvalumab in combination with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy is currently in phase III clinical development for the neoadjuvant and adjuvant treatment of resectable gastric and GEJ adenocarcinoma (MATTERHORN; NCT04592913). In this randomized, double-blind, placebo-controlled, multi-centre, global trial, durvalumab is combined with standard neoadjuvant FLOT chemotherapy before surgery and is also administered as an adjuvant treatment following resection surgery.[1] Durvalumab will be administered at a dose of 1500mg every 4 weeks (Q4W) on day 1 plus FLOT every 2 weeks (Q2W) on days 1 and 15 for four cycles (two cycles neoadjuvant and two cycles adjuvant), followed by durvalumab 1500 mg or placebo on day 1 Q4W for 10 additional cycles. Treatment will continue until confirmed disease progression or recurrence, unacceptable toxicity, withdrawal of consent, non-compliance with treatment or trial procedures, another discontinuation criterion is met, or completion of 12 cycles of adjuvant durvalumab treatment.[3]

### Key Innovation

Most patients with clinical stages II and III gastric cancer experience disease recurrence within 2 years following curative resection and chemotherapy. Therefore, there remains a need for treatment options which may offer improved outcomes for patients. Immune checkpoint inhibitors have shown a significant benefit in survival when compared with standard therapies in prospective randomised clinical trials, for various tumour types.[3] Interim analysis in the phase III MATTERHORN trial (NCT04592913) has demonstrated that durvalumab with FLOT chemotherapy for neoadjuvant treatment (before surgery) demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of pathologic complete response compared to neoadjuvant FLOT alone in patients with resectable, early-stage gastric and GEJ cancers.[4] If licensed, durvalumab in combination with FLOT chemotherapy will provide an additional neoadjuvant and adjuvant treatment option for patients with resectable gastric cancer or GEJ adenocarcinoma.

### Regulatory & Development Status

Durvalumab has Marketing Authorisation in the UK in combination with etoposide and either carboplatin or cisplatin for the first line treatment of adults with extensive-stage small cell lung cancer. Durvalumab in combination with gemcitabine and cisplatin is indicated for the first line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer.[2]

Durvalumab is in phase II and III clinical development for several other indications such as:[5]

- Hepatocellular carcinoma
- Lung cancer
- Breast cancer
- Renal cell cancer
- Bladder cancer
- Oesophageal cancer

## Patient Group

### Disease Area and Clinical Need

Gastric cancer, also called stomach cancer, is cancer that starts in any part of the stomach or the stomach wall. Most stomach cancers start in the gland cells in the inner stomach lining. These are called adenocarcinomas.[6] GEJ cancer starts at the gastro-oesophageal junction, where the food pipe (oesophagus) joins the stomach. There are three different types of GEJ cancer: type 1 is the most similar to oesophageal cancer and has spread down into the gastro-oesophageal junction from above; type 2 is centred at the actual junction; and type 3, being most similar to gastric cancer, has spread up into the junction from below.[7] Adenocarcinoma is the most common type of oesophageal cancer in the UK and usually occurs in the GEJ. Adenocarcinoma develops in the lining of cells that have changed shape and size due to long-term exposure to stomach and bile acids through gastro-oesophageal reflux.[8] Resectable cancer is when the cancer is localised and can be removed by surgery which is usually in the earlier stages of cancer.[3] Gastric cancer is more likely to manifest in men, and people over the age of 50.[9]Around 50% of all new stomach cancer cases in the UK are diagnosed in people aged 75 and over (2016-18).[6] Gastric cancer or GEJ cancer can also be linked to certain medical conditions such as gastro-oesophageal reflux disease, obesity, long term helicobacter pylori infection, Barrett's oesophagus, or gastritis.[9,10] Symptoms of gastro-oesophageal cancers can include difficulty and pain when swallowing, nausea or vomiting, heartburn, indigestion, loss of appetite, fatigue, unexplained weight loss, or a lump in the upper abdomen.[11,12]

Gastric cancer is the 17th most common cancer in the UK (2016-2018), accounting for 3% of all cancer deaths (2017-2019). Each year in the UK there are approximately 6,500 new cases of gastric cancer (2016-18), and it is predicted that 16.7% of people in England survive stomach cancer for ten years or more (2013-17).[13] In England (2021-22), there were 7,446 finished consultant episodes (FCE) for malignant neoplasms of the stomach unspecified (ICD-10 code: C16.9), with 5,830 hospital admissions that resulted in 14,744 FCE bed days and 4,400 day cases. For malignant neoplasms of the lower third of the oesophagus (ICD-10 code: 15.5) in England (2021-22), there were 23,013 FCE, with 18,788 hospital admissions that resulted in 39,228 bed days and 15,134 day cases.[14]

### Recommended Treatment Options

For resectable cancer, surgery is primarily recommended often with chemotherapy before and after surgery. Chemoradiotherapy is also an option that may be offered before surgery for those with GEJ cancer or after surgery for those with gastric cancer who did not have chemotherapy before surgery.[15,16] The National Institute for Health and Care Excellence (NICE) currently recommend nivolumab alongside chemotherapy for untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma if the tumours express PD-L1 with a combined positive score of 5 or more.[17,18] NICE also recommend adjuvant nivolumab treatment for resected oesophageal cancer or GEJ cancer in adults who have residual disease after previous neoadjuvant chemoradiotherapy.[19]

## Clinical Trial Information

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| Trial | **MATTERHORN; NCT04592913; EudraCT 2019-001555-40;** A Randomized, Double-blind, Placebo-controlled, Phase III Study of Neoadjuvant-Adjuvant Durvalumab and FLOT Chemotherapy Followed by Adjuvant Durvalumab in Patients With Resectable Gastric and Gastroesophageal Junction Cancer (GC/GEJC)<br>**Phase III** – active, not recruiting<br>**Location(s):** 8 EU countries, UK, USA, Canada, and other countries<br>**Estimated primary completion date:** February 2025 |
| Trial Design | Randomised, double-blind, placebo-controlled, parallel assignment |
| Population | N=958 (actual); patients aged ≥18 years with gastric or GEJ adenocarcinoma with resectable disease, must undergo radical surgery and no prior anti-cancer therapy for the current malignancy |
| Intervention(s) | Durvalumab 1500mg administered in combination with FLOT chemotherapy before and after surgery.[3] |
| Comparator(s) | Placebo in combination with FLOT chemotherapy |
| Outcome(s) | Primary outcome measure:<br>• Event-free survival (EFS) [Time frame: up to 5 years]. EFS is the time from date of randomisation until the date of disease progression or death.<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | The addition of durvalumab to standard neoadjuvant chemotherapy with FLOT significantly improved pathologic complete response over neoadjuvant chemotherapy alone in patients with resectable, early-stage and locally advanced gastric and GEJ cancers, meeting a key secondary end point of the trial.[20] |
| Results (safety) | The safety and tolerability of adding durvalumab to neoadjuvant FLOT chemotherapy was consistent with the known profile of this combination and did not decrease the number of patients able to undergo surgery versus chemotherapy alone.[20] |

## Estimated Cost

The National Health Service (NHS) indicative price for 1 vial of durvalumab (120mg/2.4ml concentrate for solution for infusion vials) is £592.00 (hospital only). The NHS indicative price for 1 vial of durvalumab (500mg/10ml concentrate for solution for infusion vials) is £2,466.00 (hospital only).[21]

## Relevant Guidance

### NICE Guidance

- NICE guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018. Updated July 2023.
- NICE technology appraisal. Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer (TA746). November 2021.

- NICE quality standard. Oesophago-gastric cancer (QS176). December 2018.

NHS England (Policy/Commissioning) Guidance

- 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.

Other Guidance

- National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers, Version 2.2023, NCCN Clinical Practice Guidelines in Oncology. April 2023.[22]
- European Society of Medical Oncology (ESMO). Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2016.[23]
- European Society of Medical Oncology (ESMO). Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2016.[24]
- London Cancer Alliance. LCA oesophageal and gastric cancer clinical guidelines. 2014.[25]

## Additional Information

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