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Pembrolizumab (Keytruda) for advanced gastric or gastroesophageal junction adenocarcinoma – first line

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LAY SUMMARY

Cancers of the stomach (gastric cancers) and at the intersection of the stomach and the oesophagus (gastroesophageal cancers) often start in the gland cells – these cancers are called adenocarcinomas. As the early symptoms of these adenocarcinomas can be unspecific, they are often detected late and are associated with poor life expectancy.

Pembrolizumab is an intravenously administered drug that is already approved for use in other types of cancers. It is now explored in a clinical trial as an initial (first line) treatment option for people diagnosed with advanced gastric or gastroesophageal adenocarcinomas. If licensed for use in the UK, pembrolizumab would provide a new treatment option for patients who currently have a poor life expectancy and few treatment options.

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TARGET GROUP

Gastric or gastroesophageal junction adenocarcinoma (advanced) – first line

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda; MK-3475; SCH-900475) is a humanised monoclonal antibody that blocks the interaction between programmed cell death protein-1 (PD-1) and its ligands, PD-L1 and PD-L2. Upon administration, pembrolizumab binds to PD-1, resulting in the activation of T-cell mediated immune responses against tumour cells. Instead of directly targeting tumour tissue, pembrolizumab acts as a checkpoint inhibitor to stimulate immune responses to eliminate cancer cells.[1]

Pembrolizumab is being evaluated in clinical trials for gastric or gastroesophageal junction adenocarcinoma as both first and second line therapy.[2] In the ongoing phase III trial of pembrolizumab as a first line therapy (KEYNOTE-062), participants in the active trial arms receive 200mg of pembrolizumab intravenously, as either monotherapy or in combination with chemotherapy, on the first day of each three-week cycle.[3]

Pembrolizumab is currently licensed in the EU for use in advanced (unresectable or metastatic) melanoma, and in metastatic or unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have had chemotherapy. It is also licensed in relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin (BV) treatment, or who are transplant-ineligible and have failed BV.[4] The most common side effects reported with pembrolizumab in clinical trials include fatigue, pruritus, rash, diarrhoea, and nausea.[5]

Pembrolizumab is also in clinical trials for second line treatment of gastric or gastroesophageal junction adenocarcinoma. Phase III trials of pembrolizumab are registered for head and neck cancer, colorectal cancer, multiple myeloma, bladder/renal cancer, urothelial cancer, mesothelioma, liver cancer, non-small cell lung cancer and small cell lung cancer.[6]

INNOVATION and/or ADVANTAGES

There is a substantial unmet clinical need for effective treatment options for patients with advanced gastric cancer. Considering the importance of the PD-1 pathway in gastric cancer, pembrolizumab could provide a new treatment option for this patient cohort.[7] Pembrolizumab is expected to be the first-to-market anti-PD-1 immunotherapy for this indication.

DEVELOPER

Merck Sharp & Dohme Ltd

AVAILABILITY, LAUNCH or MARKETING

In phase III clinical trials

PATIENT GROUP

BACKGROUND

Gastric cancer is a cancer that starts in the stomach, while cancer of the gastroesophageal junction (GJ) develops at the point where the oesophagus joins the stomach. GJ cancers are often hard to separate from gastric and oesophageal cancers, but are classified separately as they can behave differently to cancers of the oesophagus and stomach.[8] Most of gastric and GJ cancers start in the gland cells in the lining of the stomach or oesophagus; these cancers are called adenocarcinomas.[9]

As the initial symptoms of gastric and gastroesophageal cancers are often non-specific (including heartburn, flatulence, stomach pain, and belching) and are similar to the symptoms of other stomach conditions, these cancers are often detected late.[2,10] At an advanced stage, gastric cancer can cause unexplained weight loss, loss of appetite, bleeding, and anaemia (low red blood cell counts).[2] Most patients are diagnosed with locally advanced or metastatic disease at which point median overall survival (OS) with first line chemotherapy is only approximately 7 to 11 months.[11]

According to Cancer Research UK, 75% of stomach cancer cases in the UK are preventable. Risk factors include age, infection with Helicobacter pylori, smoking, obesity, eating excess salt, or eating too few fruit and vegetables.[12] Partly due to a reduction in H. pylori infections, reduced smoking, and improved diets, the incidence rate of gastric cancer has decreased by almost half in the UK since the early 1990s, and by more than a quarter in the last decade.[12,13] However, an increase in the number of GJ cancers in the UK has been noted; this may be related to the effect of chronic gastroesophageal reflux disease (GERD) and increased obesity (particularly Barrett's oesophagus), as both are factors linked to GJ cancers.[13,14]

CLINICAL NEED and BURDEN OF DISEASE

Gastric cancer is the 13th most common cancer in men and the 18th most common cancer in women in the UK, with 6,700 people diagnosed with the disease in 2014.[12] The cancer is twice as common in men compared to women.[2] Long-term survival remains poor, with only 15% of people diagnosed with stomach cancer in 2010-11 in England and Wales expected to survive their disease for five years or more.[12] After first line combination treatment including surgery and chemotherapy, the cancer returns in most patients and disease progression can be rapid.[14]

In 2015-16, there were 13,739 hospital admissions, 16,997 finished consultant episodes and 39,573 bed days due to malignant neoplasm of the lower third of oesophagus (ICD code: C15.5) in England.[15] In the same year there were 20,311 hospital admissions, 25,799 finished consultant episodes and 67,050 bed days due to gastric cancer (ICD codes: C16.0 – 16.9) in England.[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer (ID1096). Publication expected October 2018.

- NICE technology appraisal in development. Nivolumab for previously treated gastric or gastro-oesophageal junction cancer (ID1118). Publication expected February 2018.
- NICE technology appraisal. Ramucirumab for treating advanced gastric cancer or gastrooesophageal junction adenocarcinoma after chemotherapy (TA378). January 2016.
- NICE technology appraisal. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (TA208). November 2010.
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010.
- NICE guideline in development. Oesophago-gastric cancer. Anticipated January 2018.
- NICE guideline in development. Improving supportive and palliative care in adults, including service delivery (update). Anticipated January 2018.
- NICE interventional procedure guidance. Minimally invasive oesophagectomy. September 2011.
- NICE interventional procedure guidance. Endoscopic submucosal dissection of gastric lesions (IPG360). October 2010.
- NICE interventional procedure guidance. Laparoscopic gastrectomy for cancer (IPG269). July 2008.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Robotic assisted surgery for oesophago-gastric cancers. 2016.
- NHS England. Manual for prescribed specialised services 2016/17 Chapter 105: specialist cancer services (adults). 2016.
- 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.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and Gastric (Adult). B11/S/a.

OTHER GUIDANCE

- London Cancer Alliance. LCA Oesophageal and gastric cancer clinical guidelines. 2014.
- European Society for Medical Oncology. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2013.
- British Society of Gastroenterology. Guidelines for the management of oesophageal and gastric cancer. 2011.
- Scottish Intercollegiate Guidelines Network. Management of oesophageal and gastric cancer (87). 2006.

CURRENT TREATMENT OPTIONS

The aim of treatment for locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma is to prevent progression, extend survival, and relieve symptoms with minimal adverse effects, so as to provide patients with the best quality of life and functional capacity possible.[10,16]

People with oesophago-gastric cancer have their disease staged and discussed within an oesophago-gastric multidisciplinary team. Current treatment options include chemotherapy, radiotherapy, photodynamic therapy, and surgery. The main treatment option, if appropriate, is surgical resection of the tumour with or without adjunctive chemotherapy; these include cisplatin, capecitabine, 5FU (fluorouracil) and FOLFOX (folinic acid, fluorouracil and oxaliplatin). For many patients, curative surgery or radiotherapy is however not possible. NICE technology appraisal 191 recommends capecitabine in combination with a platinum-containing agent as an option for inoperable untreated advanced gastric cancer.[17] [18]

The prognosis for people with gastric and GJ adenocarcinomas is poor, therefore new active treatments offering improved outcomes are needed.

EFFICACY and SAFETY

Trial	Pembrolizumab as first line monotherapy vs. pembrolizumab with chemotherapy vs. placebo and chemotherapy (3 study arms), NCT02494583, KEYNOTE-062; MK-3475-062; phase III
Sponsor	Merck Sharp & Dohme Corp.
Status	Ongoing, not recruiting
Source of Information	Trial registry[3]
Location	EU (incl. UK), USA, Russia, Japan, and other countries
Design	Randomised, active/placebo-controlled, partially blinded trial
Participants	Estimated n=750; aged ≥18 years; histologically- or cytologically-confirmed diagnosis of locally advanced unresectable or metastatic gastric or GJ adenocarcinoma; HER2/neu protein negative and programmed cell death ligand 1 (PD-L1)-positive; performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) performance scale within 3 days prior to first dose of study medication
Schedule	Participants in the active trial arms receive 200mg of pembrolizumab intravenously, as either monotherapy or in combination with chemotherapy, on the first day of each three-week cycle, up to 44 months.
Follow-up	Not reported
Primary Outcomes	Overall survival Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) by Blinded Independent Central Radiologists' (BICR) review in participants treated with pembrolizumab combination therapy vs chemotherapy alone. Time Frame: Up to 44 months.
Secondary Outcomes	Overall Response Rate (ORR); Duration of Response (DOR); PFS in participants treated with pembrolizumab monotherapy; quality of life; EORTC QLQ module for gastric cancer (STO22) score
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date is reported as February 2019.

ESTIMATED COST and IMPACT

COST

Pembrolizumab is already marketed in the UK for other indications. The cost per 50mg vial is £1,315.[19] The company has agreed a patient access scheme with the Department of Health, and this scheme provides a discount to the list price of pembrolizumab. The level of the discount is commercial in confidence.[20]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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