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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab plus chemotherapy for the treatment of gastric cancer or gastro-oesophageal junction cancer – First Line

NIHRIO ID	26929	**NICE ID**	10302
Developer/Company	Merck Sharp & Dohme (UK) Ltd	**UKPS ID**	653729

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Pembrolizumab in addition to chemotherapy is being developed as first-line treatment of HER2 negative advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma in adults. 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, as there are limited treatments available once the cancer is advanced.

Pembrolizumab is an intravenously (IV) administered drug that is already approved for use in other types of cancers. Pembrolizumab is a monoclonal antibody (a protein) that binds to and blocks a specific receptor expressed on certain types of cancer. It is now being investigated in a clinical trial with chemotherapy as an initial (first line) treatment option for people diagnosed with advanced HER2 negative 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.

PROPOSED INDICATION

First-line treatment of advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma in adults.

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-347) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands programmed cell death ligand 1 and 2 (PD-L1 and PD-L2). The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[1]

In the phase III clinical trial (NCT03675737), patients receive pembrolizumab 200 mg IV on day 1 of each 21-day cycle for up to 35 cycles (approximately 2 years) + physicians' choice of either cisplatin 80 mg/m^2 IV on day 1 and 5-fluorouracil (5FU) 800 mg/m^2/day via continuous IV infusion on days 1 to 5 OR oxaliplatin 130 mg/m^2 IV on day 1 + capecitabine 1000 mg/m^2 orally twice a day (BID) on days 1 to 14.[2]

INNOVATION AND/OR ADVANTAGES

Pembrolizumab in addition to chemotherapy may offer an additional treatment option for patients with HER2 negative advanced gastric or GEJ adenocarcinoma in adults who have poor life expectancy and limited treatment options. Pembrolizumab in combination with chemotherapy is effective in increasing overall survival and progression free survival in other metastatic cancers such as advanced non–small-cell lung cancer where PD-L1 is greater than 50%, therefore it may be effective at doing the same within a population with advanced gastric or GEJ adenocarcinoma.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced in the United Kingdom (UK) both as a monotherapy and in combination with other therapeutic agents for the following indications:[1]

- As a monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults
- As a monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- As a monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ⩾50% tumour proportion score (TPS) with no epidermal growth factor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations
- In combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive tumour mutations
- In combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line

treatment of metastatic squamous non-small cell lung carcinoma in adults

- As a monotherapy for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ⩾1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYRUDA
- As monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option
- As a monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- As a monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ⩾ 10
- As a monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of metastatic or unrescetable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ⩾1
- As a monotherapy for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ⩾50% TPS and progressing on or after platinum-containing chemotherapy
- In combination with axitinib for the first-line treatment of advanced renal cell carcinoma in adults
- As monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults
- In combination with platinum and fluoropyrimidine based chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10.

In combination with chemotherapy, pembrolizumab can cause adverse effects such as anaemia, neutropenia, thrombocytopaenia, hypokalaemia, decreased appetite, dizziness, headache, peripheral neuropathy, dysgeusia, nausea, vomiting, diarrhoea, constipation, abdominal pain, rash, alopecia, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, pyrexia, oedema, increased blood creatinine.[1]

Pembrolizumab in combination with chemotherapy is currently in over 440 phase II and III clinical trials including 76 phase III trials. Some indications targeted include:[4]

- Non-small-cell lung cancer
- Triple negative breast cancer
- Metastatic oesophageal squamous cell carcinoma
- Eneoplasms
- Cervical cancer
- Urinary bladder cancer

PATIENT GROUP

DISEASE BACKGROUND

Gastric cancer is a malignant tumour originating in the cells of the stomach. There are several different types of stomach cancer. About 90-95% of stomach cancers develop in the cells of the stomach lining and are known as adenocarcinomas.[5,6] Most gastric cancers originate in the gland cells in the inner stomach lining.[6] Gastro-oesophageal junction (GEJ) cancer develops where the food pipe joins the stomach.[7] Gastric cancer begins in the stomach and can spread into the tissues around the stomach, either as locally advanced disease, or it can metastasise to other areas of the body such as the liver, lungs, lymph nodes, or the oesophagus (this is known as advanced or metastatic cancer). Advanced cancer cannot usually be cured, but treatment may control further growth of the disease, relieve symptoms and give the patient a good quality of life.[8] Gastric cancer begins with a mutation in the structure of the DNA in cells, which can affect how they grow. This means cells grow and reproduce uncontrollably, resulting in a tumour. It is not known what triggers the changes in DNA that lead to gastric cancer.[9] Overexpression of HER2 gene has been recognised as a major characteristic of gastric and GEJ cancer. Treatment guidelines vary according to weather gastic/GEJ cancer is HER2 positive or negative.[10]

Several factors which increase the risk of gastric cancer include ageing (55 years and older), male gender, smoking, severe chronic atrophic gastritis, peptic ulcers caused by Helicobacter pylori infection, diet, family history of gastric cancer, having another type of cancer, vitamin B12 deficiency, and history of stomach surgery.[9]

The initial diagnosis of gastric cancer is often delayed because up to 80% of patients are asymptomatic during the early stages of stomach cancer. Weight loss, abdominal pain, nausea and vomiting, early satiety, and peptic ulcer symptoms may accompany late-stage gastric cancer. Signs may include a palpably enlarged stomach, a primary mass (rare), an enlarged liver, Virchow's node, metastatic tumour felt on rectal examination, with growth in the rectouterine space.[11]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, gastric cancer was the 17th most common cancer in the UK. There were around 6,600 new cases of stomach cancer in the UK in 2015-2017. Around 1,300 cases of stomach cancer each year in England are linked with deprivation.[12]

More than 1 in 5 (21.6%) of people diagnosed with gastric cancer in England survive their disease for five years or more (2013-2017). It is predicted that more than 3 in 20 (16.7%) of people diagnosed with stomach cancer in England survive their disease for ten years or more (2013-2017).[13]

Gastric cancer patients with a known stage are mostly diagnosed at stage IV (46-57%). More patients with a known stage are diagnosed at a late stage (69-75% are diagnosed at stage III or IV), than an early stage (25-31% are diagnosed at stage I or II). In the UK, 35% of gastriccancer cases are in females, and 65% are in males. According to 2010-2012 data in the UK, the largest proportion of gastric cancer cases occur in the cardia next to the oesophagus.[13] In England, cancers of the gastro-oesophageal junction account for 40% of all cancers arising in the upper gastro-intestinal tract.[14]

In England, in 2020-21, there were 23,081 finished consultant episodes (FCE) and 18,625 admissions for malignant neoplasm of stomach (ICD-10 code C16), resulting in 13,560 day cases and 42,588 FCE bed days. There were also 19,664 FCE and 16,053 admissions for malignant neoplasm of abdominal part of oesophagus and lower third of oesophagus (ICD10 codes C15.2 and C15.5), resulting in 12,045 day cases and 31,242 FCE bed days.[15]

In England and Wales, in 2017, there were 3,772 deaths from malignant neoplasm of stomach (ICD-10 code C16).[16] Stomach cancer was the 14th most common cause of cancer death in the UK, accounting for 3% of all cancer deaths in 2017.[12] Latest published survival statistics for patients diagnosed in 2013 and followed up to 2017 estimate a 1-year net survival rate of 46.7% and a 5-year net survival rate of 20.6% (age-standardised).[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment depends on where in the stomach the cancer is, how big it is, whether it has spread anywhere else in the body and general health of the patient. A team of health professional should discuss the best treatment and care for each individual patient.[18]

The most common treatments for stomach cancers are surgery, chemotherapy, targeted cancer drugs and radiotherapy. The patient might have one of these treatments or a combination. Chemotherapy combined with radiotherapy is called chemoradiotherapy.[18] For example those who qualify for radical treatment undergo surgery alongside adjunctive or neojunctive chemotherapy or chemoradiotherapy. However for advanced or metastatic gastric/GEJ cancer, most treatments tend to be palliative chemotherapy.[19,20]

Chemotherapy uses anti-cancer (cytotoxic) drugs to destroy cancer cells. Chemotherapy for advanced stomach cancer can relieve the symptoms. It can also control the cancer and improve the quality of life for a time. But it cannot cure the disease. There are different chemotherapy drugs that patients might have for advanced stomach cancer. Usually the patients have a combination of 2 or 3 drugs.[21]

CURRENT TREATMENT OPTIONS

The National Institute for Health and Care Excellence (NICE) recommends trastuzumab (in combination with cisplatin and capecitabine or 5-fluorouracil) as a first line treatment option to people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. NICE also recommends palliative combination chemotherapy as a first line treatment to people with advanced oesophago-gastric cancer who have a performance status 0 to 2 and no significant comorbidities. Possible drug combinations include:[22]

- doublet treatment: 5FU or capecitabine in combination with cisplatin or oxaliplatin
- triplet treatment: 5FU or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin

PLACE OF TECHNOLOGY

If licenced, pembrolizumab plus chemotherapy will give an additional first-line palliative treatment option for adults with advanced gastric/GEJ cancer.

CLINICAL TRIAL INFORMATION

Trial	NCT03675737 2018-001757-27; Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants Gastric or Gastroesophageal

	Junction (GEJ) Adenocarcinoma (MK-3475-859/KEYNOTE-859) **Phase III** – Active, not recruiting **Locations:** 9 EU countries, UK, USA, Canada and other countries **Estimated primary completion date:** September 28, 2024
Trial design	Randomised, parallel assignment, double masking
Population	N=1542, participants over 18 years old with local advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma with known programmed cell death ligand 1 (PD-L1) expression status
Intervention(s)	200mg pembrolizumab IV
Comparator(s)	Matched placebo
Outcome(s)	Primary Outcome Measures - Overall Survival (OS) [Time Frame: Up to approximately 54 months] For full list of other outcomes, see trial record
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The list price of pembrolizumab is £2,630 per 100-mg vial. The cost of a single administration is £5,260. This represents 3 weeks of treatment.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). October 2021
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010
- NICE guideline. Oesophago-gastric cancer: assessment and management in adults NG83). January 2018

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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