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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in addition to trastuzumab and chemotherapy for HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma – First-line

NIHRIO ID	26913	**NICE ID**	10278
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	653730

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

SUMMARY

Pembrolizumab in addition to trastuzumab and chemotherapy is being developed for patients with HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma. Gastric (stomach) cancer is cancer that starts anywhere inside the stomach or the stomach wall. Advanced gastric cancer means that a cancer that began in the stomach has spread to at least one other part of the body, such as the liver or lungs. HER2-positive means the cancer cells have too much HER2 protein on the surface of their cells, which can help cancer cells to grow. Advanced or metastatic cancer cannot usually be cured and current treatment aim to control the disease, relieve symptoms, and give patients a better quality of life. Trastuzumab combined with chemotherapy is a current treatment option.

Pembrolizumab is administered by intravenous infusion and works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Trastuzumab has been designed to attach to HER2 protein which activates cells of the immune system to kill the cancer cells. Early studies have shown benefits of adding pembrolizumab to trastuzumab and chemotherapy in metastatic gastric and gastroesophageal junction cancers, and if licensed, this combination may offer an additional treatment option.

PROPOSED INDICATION

First-line treatment of human epidermal growth factor receptor 2 positive (HER2+) advanced gastric or gastroesophageal junction adenocarcinoma in adults.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody (mAb) which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands 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.[2]

Pembrolizumab in combination with trastuzumab and chemotherapy is in clinical development for the first-line treatment of participants with HER2+ advanced gastric or gastroesophageal junction adenocarcinoma in adults. In the phase III clinical trial (NCT03615326; MK-3475-811/KEYNOTE-811), patients will receive pembrolizumab 200 mg in combination with trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance dose) and standard of care chemotherapy (SOC), administered intravenously (IV) of each 3-week cycle. Details of the dosing regimen and administration schedule assessed are detailed in the clinical trial record.[1]

INNOVATION AND/OR ADVANTAGES

When added to first-line chemotherapy in patients with untreated metastatic HER2-positive esophageal, gastroesophageal junction, and gastric adenocarcinoma, the combination of pembrolizumab and trastuzumab produced a median progression-free survival of 11.3 months, and 67% of patients were progression-free at 6 months.[3]

The findings suggest there is synergy and benefit for this combination in metastatic gastric and gastroesophageal junction tumours.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:[5]

- advanced (unresectable or metastatic) melanoma in adults.
- adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
- first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- locally advanced or metastatic NSCLC 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 pembrolizumab.
- adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

- 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 monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.
- recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.

Pembrolizumab is also licensed in the UK in combination with:[5]
- pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.
- axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

The most common adverse events of pembrolizumab as monotherapy and in combination with chemotherapy (affecting more than one in ten people) include anaemia, neutropenia, thrombocytopenia, hypothyroidism, hyperthyroidism, decreased appetite, hypokalaemia, headache, dizziness, neuropathy peripheral, dysgeusia, hypertension, dyspnoea, cough, dysphonia, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, alopecia, palmar-plantar, erythrodysaesthesia syndrome, musculoskeletal pain, arthralgia, pain in extremity, fatigue, asthenia, oedema, pyrexia, blood creatinine increased, alanine aminotransferase increased, and aspartate aminotransferase increased.[2]

Pembrolizumab is currently in phase II and III clinical trials for the treatment of multiple malignant conditions such as breast cancer, colorectal cancer, prostate cancer etc.[6]

PATIENT GROUP

DISEASE BACKGROUND

Gastric cancer is a malignant tumour that originates anywhere inside the stomach or the stomach wall. There are different types of gastric cancer. Most (about 90% to 95%) cancer of the stomach are adenocarcinomas.[7] Most gastric cancers originate in the gland cells in the inner stomach lining.[8] Gastric cancer that has spread into the tissues around the stomach is known as locally advanced gastric cancer which is different to an advanced cancer. Advanced (metastatic) gastric cancer means that the cancer has spread to other areas of the body such as the liver, lungs, lymph nodes, or the oesophagus. 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.[9]

HER2 is protein involved in the pathogenesis and poor outcomes of several types of cancer, including advanced gastric cancer.[10] Tumours with increased levels of HER2 are called HER2-positive.[11] HER2-positive tumours are expected to have more aggressive characteristics than HER2-negative tumours.[12]

Several factors which increase the risk of gastric cancer include aging (50 years and older), male gender, smoking, acid reflux, gastritis, peptic ulcers caused by Helicobacter pylori infection, diet, family history of gastric cancer, having another type of cancer, overweight,

have too much salt in the diet, drink too much alcohol, do not eat enough fruit and vegetables, and eat a lot of processed meat.[13]

The initial diagnosis of gastric carcinoma is often delayed because up to 80 percent of patients are asymptomatic during the early stages the disease. 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.[14]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016, stomach cancer was the 17th most common cancer in the UK. There were around 6,700 new cases of stomach cancer in the UK in 2014-2016.[15] The age-standardised incidence rate in England for stomach cancer, in 2016, was 15.4 per 100,000 in males and 6.4 per 100,000 in females.[16]

Stomach cancer patients with a known stage are most commonly 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).[17] In the UK, 34% of stomach cancer cases are in females, and 66% are in males.[16] According to 2010-2012 data in the UK, the largest proportion of stomach cancer cases occur in the cardia, with much smaller proportions in the pyloric antrum and body of the stomach.[18]

In England, in 2018-2019, there were 26,987 finished consultant episodes (FCE) for malignant neoplasm of stomach (ICD 10: C16), resulting in 21,425 hospital admissions and 60,314 FCE bed days.[19]

According to 2010-2011 data, 19% of people diagnosed with stomach cancer in England and Wales survive their disease for five years or more.[20] Around 5 out of 100 people (5%) with stage 4 stomach cancer will survive for 5 years or more after they are diagnosed.[21]

Stomach cancer was the 14th most common cause of cancer death in the UK in 2017. Crude mortality rate in England was 6.2 per 100,000 in 2017.[22] Stomach cancer mortality is strongly related to age, with the highest mortality rates being in older people.[23] In the 2017 death registration in England and Wales, there were 3,772 deaths (2,444 males, 1,328 females) due to malignant neoplasm of stomach (C16) with the higher proportions in aged 65 and above.[24]

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.[25]

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.[25]

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.[26]

CURRENT TREATMENT OPTIONS

NICE recommendation about first-line palliative chemotherapy for locally advanced or metastatic oesophago-gastric cancer treatment include:[27]

- Trastuzumab (in combination with cisplatin and capecitabine or 5-fluorouracil) is recommended as a treatment option to people with HER2+ metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:
  - have not received prior treatment for their metastatic disease and have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in combination with trastuzumab and chemotherapy will offer an additional option for the first-line treatment of patients with HER2+ advanced gastric or gastroesophageal junction adenocarcinoma.

CLINICAL TRIAL INFORMATION

Trial	MK-3475-811/KEYNOTE-811, NCT03615326, 3475-811, EudraCT 2018-000224-34; adults aged ≥18 years; pembrolizumab vs placebo, both in combination with trastuzumab and chemotherapy; phase III
Sponsor	Merck Sharp & Dohme Corp.
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (including the UK), United States and other countries
Design	Randomised, placebo-controlled, double-blind
Participants	n= 732 (planned); aged ≥18 years old; has a histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma; HER2-positive defined as either immunohistochemistry (IHC) 3+ or IHC 2+ in combination with in-situ hybridization positive (ISH+) or fluorescent in-situ hybridization (FISH); has measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 as determined by the site investigator; has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) performance scale within 3 days prior to the first dose of trial treatment; has a life expectancy of greater than 6 months; and has adequate organ function.
Schedule	Participants were randomised to receive: - Pembrolizumab 200 mg intravenously (IV) on day 1 of each 3-week cycle;Trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance dose) will be administered IV on day 1 of each 3-week cycle.

	- Placebo to pembrolizumab (saline) IV on day 1 of each 3-week cycle. Trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance dose) will be administered IV on day 1 of each 3-week cycle. Standard of care (SOC) chemotherapy for the global cohort will either be FP (80 mg/m^2 cisplatin administered IV on Day 1 of each 3-week cycle and 800 mg/m^2 5-fluorouracil (5-FU) administered IV on Days 1-5 of each 3-week cycle) or CAPOX (1000 mg/m^2 capecitabine administered orally twice daily (BID) on days 1-14 of each 3-week cycle and 130 mg/m^2 oxaliplatin administered IV on Day 1 of each 3-week cycle). A Japan cohort will receive SOX chemotherapy consisting of S-1 (tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo)) administered orally BID according to body surface area (BSA) on Days 1-14 of each 3-week cycle and oxaliplatin (130 mg/m^2) administered IV on Day 1 each 3-week cycle.
Follow-up	Up to 5 years
Primary Outcomes	• Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR [Time frame: up to 4 years] • Overall Survival (OS) [Time frame: up to 5 years]
Secondary Outcomes	• Objective Response Rate (ORR) per RECIST 1.1 assessed by BICR [Time frame: up to 5 years] • Duration of Response (DOR) per RECIST 1.1 assessed by BICR [Time frame: up to 5 years] • Adverse event (AE) [Time frame: up to 5 years] • Treatment discontinuations due to AEs [Time frame: up to 5 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as June 2023.

ESTIMATED COST

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[28]
- A 100 mg/4 ml concentrate for solution for infusion vial costs £2630.00
- A 50 mg powder for concentrate for solution for infusion vial costs £1315.00

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer (ID1096). Expected publication: TBC
- NICE technology appraisal guidance. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (TA208). November 2010.
- NICE guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.
- NICE quality standards. Oesophago-gastric cancer (QS176). December 2018.

- NICE interventional procedure guidance. Minimally invasive oesophagectomy (IPG407). September 2011.

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). Published date to be confirmed.
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- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European Society of Medical Oncology. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[29]

ADDITIONAL INFORMATION

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