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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in addition to chemotherapy for perioperative treatment of gastric or gastro-oesophageal junction adenocarcinoma

NIHRIO ID	22774	**NICE ID**	10174
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	651361

Licensing and market availability plans	Currently in phase III trial.

SUMMARY

Pembrolizumab in addition to chemotherapy is in clinical development for gastric or gastro-oesophageal junction cancer. Gastric cancer is cancer that starts anywhere inside the stomach or the stomach wall. Initial symptoms of disease are similar to other stomach conditions but symptoms of advanced stages may include a lack of appetite and subsequent weight loss; fluid in the abdomen and blood in the stool. Because of the nature of symptoms, gastric cancer is often diagnosed at an advanced stage. Surgery is a treatment option and often combined with chemotherapy given before (neo-adjuvant) and after (adjuvant) the surgery to improve treatment outcomes.

Pembrolizumab, is a monoclonal antibody, a protein that has been designed to recognise and block a receptor called PD-1. By blocking PD-1, pembrolizumab stops the cancer switching off immune cells, thereby increasing the immune system's ability to kill the cancer cells. The addition of pembrolizumab to chemotherapy in the neo-adjuvant/adjuvant setting may benefit patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma as positive results have been found in studies on other types of cancers.

PROPOSED INDICATION

Perioperative treatment of patients with locally advanced resectable gastric or gastro-oesophageal junction (GEJ) adenocarcinoma[a]

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.[1]

Pembrolizumab in addition to chemotherapy is in clinical development for previously untreated gastric and GEJ adenocarcinoma, neo-adjuvant (prior to surgery) or adjuvant (after surgery). In the phase III clinical trial (NCT03221426; MK-3475-585/KEYNOTE-585), neo-adjuvant participants will receive 3 cycles of 200mg pembrolizumab on day 1 of each 3-week cycle (Q3W).[2] Adjuvant participants 4 to 10 weeks post-surgery, will receive pembrolizumab 200 mg via IV infusion on day 1 Q3W of each 3-week cycle.[2]

INNOVATION AND/OR ADVANTAGES

Despite widespread adoption of multimodality perioperative treatment strategies for gastric cancer, 5-year overall survival rates remain low.[3]

Given the potentially harmful effects of multiple chemotherapy treatment regimens on the immune system, application of PD-1 pathway blockade earlier in a disease course before a tumour metastasises may significantly enhance a drug's ability to induce immune-mediated cancer regression. It has also been shown that after neoadjuvant therapy, there is a consistent trend for chemoradiation to induce more tumour-infiltrating lymphocytes. The appearance of these microenvironment features after induction therapy suggests that a tumour will respond favourably to immune-based therapy and, in particular, to PD-1–based checkpoint blockade. More so, PD-L1 upregulation occurs in approximately 40% of gastroesophageal cancers.[4]

Combining chemotherapy with pembrolizumab in the neoadjuvant/adjuvant setting may benefit patients with locally advanced, resectable disease.[3] Preliminary data suggested this combination had manageable toxicity profiles and given the positive results from a lung cancer trial of pembrolizumab plus chemotherapy, it is hoped that they will be similar in Gastric and GEJ adenocarcinoma.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:[1]

- advanced (unresectable or metastatic) melanoma in adults
- as an adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection

[a] Information provided by Merck Sharp & Dohme Ltd on UK PharmaScan

- 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 – first line
- locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen
- 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 ≥ 10
- recurrent or metastatic head and neck squamous cell carcinoma (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:[1]

- pemetrexed and platinum chemotherapy 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 for the first-line treatment of metastatic squamous NSCLC in adults.[1]

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, decreased appetite, diarrhoea, nausea, vomiting, constipation, rash, pruritus, fatigue, asthenia, oedema, dysgeusia, and increased alanine aminotransferase.[1]

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.[5]

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. More than 95% of stomach cancers develop in the cells of the stomach lining and are known as adenocarcinomas.[6,7] Most gastric cancers originate in the gland cells in the inner stomach lining.[8] Advanced gastric cancer begins in the stomach and 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. 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.[6] 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.[10] Gastric cancer can involve loss of the tumour suppression gene, p53.[9]

Several factors which increase the risk of gastric cancer include aging (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.[10]

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.[11]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016, gastric 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. The age-standardised incidence rate in England for malignant neoplasm of the stomach, in 2016, was 15.4 per 100,000 in males and 6.4 per 100,000 in females.[12]

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).[12] There were 5,712 diagnosis for stage 4 stomach cancer in England between 2013 and 2015.[13]

In the UK, 34% of stomach cancer cases in the UK are in females, and 66% 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).[12] 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 2017-2018, there were 25,409 finished consultant episodes (FCE) for malignant neoplasm of stomach (ICD 10: C16), resulting in 19,873 hospital admissions and 60,252 FCE bed days.[15]

According to 2010-2011 data, 19% of people diagnosed with stomach cancer in England and Wales survive their disease for five years or more.[16] Five year survival rates for stage III (A, B, C) gastric cancer were 25%, 20%, and 10% respectively; whereas stage IV was 5%.[17]

Gastric cancer was the 14th most common cause of cancer death in the UK in 2016. Crude mortality rate in England was 6.6 per 100,000 in 2014. Gastric cancer mortality is strongly related to age, with the highest mortality rates being in older males and females.[18] In the 2017 death registration in England and Wales, there were 3,772 deaths (2,444 males, 1,328 males) due to malignant neoplasm of stomach (C18) with the higher proportions in aged 65 and above.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The most common treatments for gastric cancers are surgery, radiotherapy, and chemotherapy. The patient may have one of these treatments or a combination. If the tumour is in the upper part of the stomach, the patient may also have radiotherapy prior to surgery. If surgery is recommended, the patient may have chemotherapy beforehand. If it is not possible to remove the tumour completely, then the treatment focus will be on preventing the tumour from getting any bigger and causing further harm to the body. This can be done by surgery (palliative surgery) or by chemotherapy. When it is not possible to eliminate the cancer or slow it down, the aim of treatment will be to relieve the symptoms by surgery or radiotherapy.[20,21]

For stomach cancer, chemotherapy might be given to the patient before surgery to reduce the amount of cancer that has to be removed during the operation. Chemotherapy can also be used after surgery to destroy any remaining cancer cells and prevent the cancer from coming back.[21]

CURRENT TREATMENT OPTIONS

NICE recommendation for neoadjuvant and adjuvant treatment include:[22]

- People with localised oesophageal and gastro-oesophageal junctional adenocarcinoma (excluding T1N0 tumours) who are going to have surgical resection should be offered a choice of:
  - Chemotherapy, before or before and after surgery or
  - Chemoradiotherapy, before surgery.

- For gastric cancer:
  - Chemotherapy before and after surgery to people with gastric cancer who are having radical surgical resection.
  - Chemotherapy or chemoradiotherapy after surgery for people with gastric cancer who did not have chemotherapy before surgery with curative intent

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in addition to chemotherapy will offer an additional perioperative treatment option to patients with locally advanced resectable gastric or gastro-oesophageal junction adenocarcinoma.

CLINICAL TRIAL INFORMATION

Trial	**MK-3475-585, KEYNOTE-585,** NCT03221426, EudraCT_2016-004408-76; pembrolizumab vs placebo, both in combination with chemotherapy; phase III
Sponsor	Merck Sharp and Dohme Corp
Status	Ongoing
Source of Information	Trial registry[2], Journal article[3]
Location	6 EU countries, incl UK, USA, Canada and other countries
Design	Randomised; placebo-controlled; double-blind
Participants	N=860 (planned); aged 18 years and older; has previously untreated localized gastric or GEJ adenocarcinoma; plans to proceed to surgery following pre-operative chemotherapy; has life expectancy of greater than 6 months; has an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1 within 3 days prior to the first dose of study treatment.
Schedule	Randomised to: • Pembrolizumab+Chemotherapy ○ Neoadjuvant participants will receive 3 cycles of 200mg pembrolizumab in addition to 80 mg/m^2 cisplatin via intravenous (IV) infusion on day 1 of each 3-week cycle (Q3W) and capecitabine 1000 mg/m^2 via oral tablets twice each day (BID) on days 1 to 14 of each 3-week cycle or 80 mg/m^2 cisplatin via IV

	infusion on day 1 Q3W and 5-fluorouracil (5FU) via continuous IV infusion on Days 1 to 5 of each 3-week cycle. ○ Adjuvant participants 4 to 10 weeks post-surgery, will receive pembrolizumab 200 mg via IV infusion on day 1 Q3W in addition to IV cisplatin 80 mg/m^2 on day 1 Q3W and capecitabine 1000 mg/m^2 via oral tablets BID on days 1 to 14 of each 3-week cycle or cisplatin 80 mg/m^2 via IV infusion on day 1 Q3W and 5FU via continuous IV infusion on days 1 to 5 of each 3-week cycle for up to 14 cycles • Placebo ○ Neoadjuvant participants receive 3 cycles of placebo (normal saline solution) via IV infusion on Day 1 Q3W PLUS cisplatin 80 mg/m^2 via IV infusion on Day 1 Q3W and capecitabine 1000 mg/m^2 via oral tablets BID on Days 1 to 14 of each 3-week cycle OR cisplatin 80 mg/m^2 via IV infusion on Day 1 Q3W and 5FU via continuous IV infusion on Days 1 to 5 of each 3-week cycle. ○ Adjuvant: 4 to 10 weeks post-surgery, participants receive placebo via IV infusion on Day 1 Q3W PLUS cisplatin 80 mg/m^2 via IV infusion on Day 1 Q3W and capecitabine 1000 mg/m^2 via oral tablets BID on Days 1 to 14 of each 3-week cycle OR cisplatin 80 mg/m^2 via IV infusion on Day 1 Q3W and 5FU via continuous IV infusion on Days 1 to 5 of each 3-week cycle for up to 14 cycles. There is a safety cohort to evaluate 5-fluorouracil plus docetaxel plus oxaliplatin plus leucovorin (FLOT) as a potential chemotherapy backbone option. In the FLOT safety cohort, eligible patients will be randomly assigned in a 1:1 ratio to receive pembrolizumab or placebo in combination with FLOT. FLOT regimen might be incorporated as one of the chemotherapy backbone options in the main study if adequate safety is demonstrated in combination with pembrolizumab. Neoadjuvant participants receive pembrolizumab in addition to docetaxel 50 mg/m^2 via IV infusion, oxaliplatin 85 mg/m^2 via IV infusion, 5FU 2600 mg/m^2 via IV infusion, and leucovorin (calcium folinate) 200 mg/m^2 via IV infusion Q2W (on days 1 and 15 of cycle 1; day 8 of cycle 2, and day 1 of cycle 3) for 4 administrations. Adjuvant participants will receive pembrolizumab 200 mg via IV infusion day 1 Q3W for up to 11 cycles in addition to docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, 5FU 2600 mg/m^2, and leucovorin 200 mg/m^2 Q2W (on days 1 and 15 of cycle 1; day 8 of cycle 2, and day 1 of Cycle 3) for 4 administrations.
Follow-up	6 years
Primary Outcomes	• Overall survival (OS) [Time frame: up to approximately 2 years] • Event-free survival (EFS) [Time frame: up to approximately 2 years] • Pathological complete response (pathCR) rate [Time frame: up to 6 weeks after completion of 3 cycles of neoadjuvant treatment (up to 15 weeks)] • Adverse Events (AEs) [Time frame: up to approximately 27 months] • Study treatment discontinuations due to AEs [Time frame: up to approximately 2 years]
Secondary Outcomes	Disease-free survival (DFS) [Time frame: Up to approximately 2 years]

Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as July 2023

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate for solution for infusion vial (25mg/ml) costs £2,630, and 50mg powder for concentrate for solution for infusion vial costs £1,315.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pertuzumab for untreated metastatic HER2-
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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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