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Avelumab for gastric and gastroesophageal junction adenocarcinoma – third 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.

Avelumab is a new drug that could induce an immune response against tumour cells. It is in clinical trials for several different cancers, including gastric and gastroesophageal adenocarcinoma. One trial is currently exploring its use as a third line treatment for these cancers, for patients who have already received two other courses of therapy that have failed. It is given as one hour drip straight into a patient's vein once every two weeks. If licensed for use in the UK, it could offer a novel treatment option for patients for whom other cancer treatments have not worked.

TARGET GROUP

Gastric or gastroesophageal junction adenocarcinoma: unresectable, locally advanced or metastatic – third line with best supportive care

TECHNOLOGY

DESCRIPTION

Avelumab (MSB0010718C; PF06834635) is a fully-human, programmed cell death ligand 1 monoclonal antibody (anti-PD-L1 IgG1).[1] It binds to PD-L1, a protein produced by several cancers, and inhibits the interaction between PD-L1 and PD-1, thereby removing the suppressive effects of PD-L1 on anti-tumour CD8+ T cells.[1] This results in the activation of cytotoxic T-cells and the adaptive immune system.[1] By attaching to cancer cells, avelumab makes them a target for attack by immune system cells called natural killer cells, and could impact the growth of cancer.[2]

Avelumab is in phase III clinical trials for gastric and gastroesophageal junction adenocarcinoma. In the ongoing trial, avelumab is administered as a one-hour intravenous (IV) infusion at 10 mg per kilogram once every two weeks.[3]

Avelumab has been launched as a second-line treatment for metastatic Merkel cell carcinoma in the USA in March 2017 and for urothelial cancer in May 2017. Regulatory submissions have also been made for Merkel cell carcinoma in the EU.[1] Avelumab is also in stage III clinical trials for: diffuse large B cell lymphoma, head and neck cancer, non-small cell lung cancer, ovarian cancer, and renal cell carcinoma.[1] It is in phase II clinical trials for: endometrial cancer, gestational trophoblastic disease, glioblastoma, intestinal cancer, nasopharyngeal cancer, recurrent respiratory papillomatosis, and thymoma.

In a trial for the US-licensed indication, Merkel cell carcinoma, treatment-related adverse events were experienced by 71% of patients, with the most common adverse events being fatigue and infusion-related reactions.[1] The FDA lists the most common serious adverse reactions to avelumab as being immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, adrenal insufficiency, hypo- and hyperthyroidism, diabetes mellitus, and nephritis) as well as life-threatening infusion reactions.[4]

INNOVATION and/or ADVANTAGES

If licensed for this indication and patient cohort, avelumab could offer an additional treatment option for a group of patients who currently have a very poor prognosis following the failure of other treatment options (both first and second line therapy). Alternatives to chemotherapy with lower toxicity would be important for this patient cohort due to their already poor performance status following prior treatment. The ongoing clinical trial explores whether overall survival of these patients will improve following avelumab immunotherapy.

DEVELOPER

Merck Serono Ltd; Pfizer

AVAILABILITY, LAUNCH or MARKETING

Avelumab was designated an orphan drug in the EU for gastric cancer in December 2016.[5] The manufacturer is trialling avelumab as both first and third line treatment for this indication.[6]

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.[7] Most of gastric and GJ cancers start in the gland cells in the lining of the stomach or oesophagus; these cancers are called adenocarcinomas.[8]

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.[2,9] 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.[10]

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, and eating excess salt, or eating too little fruit and vegetables.[11] 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.[11,12] 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.[12,13]

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.[11] 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.[11]

After first-line combination treatment including surgery and chemotherapy, the cancer returns in most patients and disease progression can be rapid.[13] Almost half of patients do not benefit from second-line chemotherapy or suffer from chemotherapy toxicity.[13] A recent narrative review notes that "only a small percentage of patients" continue to have a good performance status after second-line therapy for the indication and are still medically fit to be offered further therapy.[14] Exact information on the number of patients who would be eligible for third line treatment annually could not be obtained.

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. Avelumab for merkel cell carcinoma [ID1102]. Publication expected February 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. 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-ESSO-ESTRO clinical practice guidelines. 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.[9,16] Current treatment options include chemotherapy, palliative radiotherapy and palliative surgery.[16] However in terms of third line therapy, very limited literature supports the use of chemotherapy.[17]

Clinical experts have expressed a particular need for new treatment agents for patients whose disease has progressed following prior chemotherapy.[18] The prognosis for people with gastric and GEJ adenocarcinomas is poor, therefore new active treatments offering improved outcomes are needed.

EFFICACY and SAFETY

Trial	JAVELIN Gastric 300; avelumab vs. chemotherapy as third line therapy (with best supportive care); NCT02625623; phase III
Sponsor	EMD Serono Research & Development Institute; Merck KGaA
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (not incl. UK), USA, Australia, and other countries
Design	Randomised, active-controlled trial
Participants	Estimated n=330; adults 18 years and older; patients with histologically confirmed recurrent unresectable, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. Subjects must have received two prior courses of systemic treatment, and must have progressed after the second line.
Schedule	All subjects in both arms will receive best supportive care (BSC) as background therapy. Subjects will receive BSC with either avelumab or physician's choice chemotherapy (from a prespecified list of therapeutic options) or BSC alone with no active therapy. Avelumab will be administered as a 1-hour intravenous (IV) infusion at 10 milligram per kilogram (mg/kg) once every 2-week treatment cycle until confirmed disease progression or unacceptable toxicity.
Follow-up	5 years
Primary Outcomes	Overall survival time
Secondary Outcomes	Progression free survival; best overall response; quality of life; safety and tolerability
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as August 2017.

ESTIMATED COST and IMPACT

COST

The cost of avelumab is not yet known.

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

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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