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HEALTH TECHNOLOGY BRIEFING
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Rivoceranib for locally advanced or metastatic gastric or gastro-oesophageal junction cancer - after two or more therapies

NIHRIO ID	4700	**NICE ID**	9674
Developer/Company	Elevar Therapeutics	**UKPS ID**	Not Available

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

SUMMARY

Rivoceranib is in clinical development for locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction cancer that has progressed since last treatment with at least two prior lines of therapies. Gastric cancer is cancer that starts anywhere in the stomach. Cancer that starts between the oesophagus (food pipe) and the stomach is gastro-oesophageal junction cancer. Locally advanced cancer means that the cancer has spread into the tissues around the stomach. Advanced or metastatic means where the cancer has spread to another part of the body such as the liver or lungs. Advanced cancers have a poor prognosis and often have no cure, but treatment may control the cancer, relieve symptoms and give the patient a good quality of life.

Rivoceranib is an oral medicine with potential anti-tumour activities. It works by binding to a receptor responsible for preventing cell movement and multiplication and decrease the tumour mass. If licensed, rivoceranib will provide an additional treatment option for patients with locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction cancer that has progressed since last treatment with at least two prior lines of therapies.

PROPOSED INDICATION

Patients with locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction cancer that has progressed since last treatment with at least two prior lines of therapies[1,a]

TECHNOLOGY

DESCRIPTION

Rivoceranib (Apatinib, YN968D1) is a selective potent inhibitor of vascular endothelial growth factor receptor-2 (known as VEGFR2) which mediates the primary pathway for tumour-mediated angiogenesis.[2] Rivoceranib selectively binds to and inhibits vascular endothelial growth factor receptor 2, which may inhibit VEGF-stimulated endothelial cell migration and proliferation and decrease tumour microvessel density.[3]

Rivoceranib is in clinical development for the treatment of patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction cancer that has progressed since the last treatment with at least two prior lines of therapies. In the phase III clinical trial (NCT03042611; ANGEL), patients will receive a daily oral dose of rivoceranib plus best supportive care defined as palliative non-cancer therapy at the investigator's discretion.[1]

INNOVATION AND/OR ADVANTAGES

Rivoceranib has shown potential to improve outcomes in combination with chemotherapeutics and immunotherapy, as well as for maintenance therapy.[2] Studies have reported rivoceranib prolonged the median overall-survival (OS) and median progression-free survival (PFS) of gastric cancer patients who have failed in two or more lines of treatments regimens in the pivotal phase III trial in China (4.7 vs 6.5 months for OS, and 1.8 vs 2.6 months for PFS in the placebo and intervention groups respectively).[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Rivoceranib does not currently have Market Authorisation for any indication in the EU/UK.

Rivoceranib is currently in phase II clinical development for recurrent or metastatic adenoid cystic carcinoma, sarcoma and in phase I/II for metastatic colorectal cancer.[5]

Rivoceranib received an orphan from European Medicine Agency (EU/3/17/1840) for the treatment of gastric cancer in 2017.[6]

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.[7,8] Most gastric cancers originate in the gland cells in the inner stomach lining.[9] While gastro-oesophageal junction cancer develops where the food pipe joins the stomach.[10] 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

[a] Information provided by Elevar Therapeutics

other areas of the body such as the liver, lungs, lymph nodes, or the oesophagus (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.[7] 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.[11] Gastric cancer can involve loss of the tumour suppressor gene, p53.[12]

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.[11]

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.[13]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, gastric cancer was the 17th most common cancer in the UK. There were around 6,595 new cases of stomach cancer in the UK in 2015-2017. The age-standardised incidence rate in England for malignant neoplasm of the stomach, in 2017, was 14.4 per 100,000 in males and 6.2 per 100,000 in females.[14]

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).[14] In the UK, 35% of stomach cancer 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).[14] In England, cancers of the gastro-oesophageal junction account for 40% of all cancers arising in the upper gastro-intestinal tract.[15]

In England, in 2018-2019, there were 26,987 finished consultant episodes (FCE) for malignant neoplasm of stomach (ICD-10 code: C16), resulting in 21,425 hospital admissions and 60,314 FCE bed days and 15,869 day cases.[16]

In England and Wales, in 2017, there were 3,772 deaths from malignant neoplasm of stomach (ICD-10 code: C16).[17] Stomach cancer was the 14th most common cause of cancer death in the UK, accounting for 3% of all cancer deaths in 2017.[14] Latest published survival statistics (patients diagnosed in 2013-2017) report a 1-year net survival rate of 47.4 % and a 5-year net survival rate of 21.6% (age-standardised).[18]

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.[19]

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.[19]

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.[20]

CURRENT TREATMENT OPTIONS

Lonsurf (trifluridine /tipiracil hydrochloride) is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease.[21] Trifluridine–tipiracil is currently undergoing NICE technology appraisal for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies.[22]

PLACE OF TECHNOLOGY

If licensed, rivoceranib will provide an additional treatment option for patients with locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction cancer that has progressed since last treatment with at least two prior lines of therapies.

CLINICAL TRIAL INFORMATION

Trial	ANGEL; NCT03042611; Prospective, randomized, double-blinded, placebo-controlled, multinational, multicenter, parallel-group, phase III study to evaluate the efficacy and safety of apatinib plus best supportive care (BSC) compared to placebo plus BSC in patients with advanced or metastatic gastric cancer **Phase III**- Ongoing **Location(s):** EU (Including UK), USA and other countries.
Trial design	Randomised, parallel assignment, double-blinded
Population	N=460; aged 18 and older; male or female; locally advanced, unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction
Intervention(s)	Rivoceranib; daily oral dose of rivoceranib plus best supportive care defined as palliative non-cancer therapy at the Investigator's discretion
Comparator(s)	Placebo; daily oral dose of placebo with best supportive care defined as palliative non-cancer therapy at the Investigator's discretion
Outcome(s)	Overall survival (Time frame: Time from randomisation until death, assessed up to approximately 18 months) See trial record for full list of other outcomes.

Results (efficacy)	Patients who received rivoceranib achieved longer median OS, but the difference did not reach statistical significance (5.8 months vs. 5.1 months; HR = 0.93; 95% CI, 0.74-1.15). However, rivoceranib-treated patients did achieve significantly longer median PFS (2.83 months vs. 1.77 months; HR = 0.57; 95% CI, 0.46-0.79), a higher objective response rate (6.87% vs. 0%; *P* = 0.002), and a higher disease control rate (42.4% vs. 13.1%; *P* < 0.0001). Additionally, rivoceranib significantly increased OS among patients being treated in the fourth-line setting (6.43 months vs. 4.73 months; HR = 0.65; 95% CI, 0.46-0.92).[23]
Results (safety)	The most common treatment-related adverse events experienced by rivoceranib-treated patients included the mechanism-of-action-related events of hypertension (34.2%), proteinuria (29.3%), and hand-foot skin reaction (26.4%).[23]

ESTIMATED COST

The estimated cost of rivoceranib is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after two or more therapies (ID1507). Expected publication date: TBC
- NICE technology appraisal in development. Pembrolizumab for previously treated metastatic gastric or gastro-oesophageal junction cancer (ID1168). Expected publication date: TBC.
- 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

- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and gastric (Adult). B11/S/a.
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- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Robotic assisted surgery for oesophago-gastric cancers. 16006/P. July 2016.

OTHER GUIDANCE

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- European Society for Medical Oncology (ESMO) Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[25]

- London Cancer Alliance (LCA). LCA Oesophageal and Gastric Cancer Clinical Guidelines. 2014.[26]
- Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. 2011.[27]

ADDITIONAL INFORMATION

Elevar Therapeutics, did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision-making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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