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Health Technology Briefing
June 2024

Bemarituzumab with chemotherapy for previously untreated advanced gastric or gastroesophageal junction cancer

Company/Developer	Amgen Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26965	NICE ID: Not available	UKPS ID: 674888

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Bemarituzumab in combination with chemotherapy is in clinical development for the treatment of previously untreated locally advanced, or metastatic gastric or gastroesophageal junction (GEJ) cancer. Gastric (or stomach) cancer is when abnormal cells in the stomach start to grow and divide in an uncontrolled way. GEJ cancer starts in the junction where the food pipe joins the stomach. Locally advanced means that cancer has grown outside the body part where it started but has not yet spread to other parts of the body; metastatic cancer is cancer that has spread from the place it first formed to another part of the body. Gastric cancer, including GEJ cancer, is often diagnosed at an advanced stage and is therefore associated with poor outcomes. There remains an unmet need for new and effective treatment options that target the proteins that are expressed in these cancers to improve health outcomes.

Bemarituzumab is a novel monoclonal antibody, a protein that has been designed to recognise and block a protein called FGFR2b which is involved in numerous cellular functions. By blocking FGFR2b, bemarituzumab prevents further tumour growth and enhances the body's immune response against the cancer cells. Bemarituzumab is administered intravenously. If licensed, bemarituzumab in combination with chemotherapy will provide an additional first-line treatment option for patients with locally advanced or metastatic gastric or GEJ cancer.

Proposed Indication

Treatment of adult patients with previously untreated locally advanced or metastatic gastric or gastroesophageal junction (GEJ) cancer with FGFR2b (fibroblast growth factor receptor 2b) overexpression. [1]

Technology

Description

Bemarituzumab (AMG 552) is a recombinant, afucosylated, humanised, IgG1 kappa monoclonal antibody that binds to the extracellular domain of fibroblast growth factor receptor 2b (FGFR2b). Bemarituzumab inhibits the activation of FGFR2b, and has enhanced antibody-dependent cellular cytotoxicity against tumour cells that express FGFR2b.[2,3] FGFR2b is a receptor tyrosine kinase primarily expressed on epithelial cells and involved in numerous cellular functions.[4]

Bemarituzumab with chemotherapy is currently in clinical development for the treatment of patients with unresectable, locally advanced, or metastatic gastric or GEJ cancer. In the phase III clinical trial (FORTITUDE-101; NCT05052801), patients will be administered bemarituzumab 15 mg/kg every 2 weeks with an additional 7.5 mg/kg dose on cycle 1 day 8 as intravenous (IV) infusion, in combination with chemotherapy (mFOLFOX6) administered at a fixed dose every 2 weeks as IV infusion.[1,5]

Key Innovation

Eighty percent to ninety percent of people with gastric cancer are either diagnosed at an advanced stage when the tumour is inoperable, or develop a recurrence within five years after surgery.[6] Consequently, outcomes are poor in these patients.[7] Recent therapeutic approaches including immune checkpoint inhibitors or targeted therapies that are directed towards different mechanistic pathways of gastric cancer have demonstrated promising outcomes, especially in biomarker-enriched patient populations.[8]

The FGFR signalling pathway is integral to cellular activities, including proliferation, differentiation, and survival. Dysregulation of this pathway is implicated in numerous human cancers, positioning FGFR as a prominent therapeutic target. Bemarituzumab specifically targets FGFR2b overexpression. It exhibits a dual mechanism of action, involving the inhibition of FGFR2b signalling and the enhancement of antibody-dependent cell-mediated cytotoxicity. The administration of targeted therapies such as bemarituzumab can be administered in conjunction with chemotherapy in clinical settings to optimise therapeutic efficacy by selectively targeting molecular pathways while simultaneously utilising the broad cytotoxic effects of chemotherapeutic agents.[9] If licensed, bemarituzumab in combination with chemotherapy will offer an additional treatment option for patients with previously untreated, unresectable, locally advanced or metastatic gastric or GEJ cancer with FGFR2b overexpression.

Regulatory & Development Status

Bemarituzumab does not currently have Marketing Authorisation in the UK/EU for any indication.

Bemarituzumab is in phase Ib/II clinical development for solid tumours.[10]

Bemarituzumab has the following designations:[11,12]

- A Breakthrough Therapy by the US FDA in April 2021
- An orphan drug in the USA in 2016 for treatment of gastric cancer including cancer of the GEJ.

Patient Group

Disease Area and Clinical Need

Gastric cancer (also known as stomach cancer) is when abnormal cells in the stomach start to grow and divide in an uncontrolled way.[13] Most stomach cancers start in the gland cells in the inner stomach lining, and these are called adenocarcinomas.[13] The GEJ is where the food pipe (oesophagus) joins the stomach; the cancer that starts here is called GEJ cancer.[14] FGFR2b is a protein that is expressed in gastric cancers and other cancerous tumours.[4] Locally advanced cancer is cancer that has grown into the tissues around the stomach, or into nearby organs.[15] Unresectable cancer is that which cannot be removed completely through surgery. This can be the case for a variety of reasons, including tumour size, stage, and location.[16] For metastatic cancers, the cancer cells break away from the original (primary) tumour, travel through the blood or lymph system, and form a new tumour in other organs or tissues of the body.[17] The most common symptoms of stomach cancers include difficulty swallowing, unexplained weight loss, stomach pain, indigestion, appetite loss, nausea and tiredness.[18] The causes of most stomach cancers are unknown, however, risk factors include age, obesity and smoking. Infection with *Helicobacter pylori* is also an important risk factor, causing around 40% of stomach cancers in the UK.[19]

There are around 6,500 new stomach cancer cases in the UK every year (2016-2018). Stomach cancer is the 17th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-2018).[20] The age standardised incidence rate of stomach cancer in England is 14.6 and 6.4 per 100,000 amongst males and females respectively.[21] In England (2022-23), there were 7,100 finished consultant episodes (FCE) and 5,602 admissions for malignant neoplasm: Malignant neoplasm of the stomach (unspecified; ICD-10 code C16.9), resulted in 4,241 day cases and 14,663 FCE bed days. For malignant neoplasms of the lower third of the oesophagus (ICD-10 code C15.5), in England (2022-23), there were 24,753 FCE and 20,849 admissions that resulted in 17,148 day cases and 40,640 bed days.[22] For patients diagnosed in England between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for stage III stomach cancer were 63.2% and 23.5% respectively, and the 1-year survival rate for stage IV stomach cancer is 21.4%.[23] For stomach cancer, all stages age standardised 1-year overall survival is 47.4%, and 5-year overall survival is 21.6%. For stomach cancer, stage III, age standardised 1-year and 5-year overall survival is 63.2% and 23.5%.[23]

Recommended Treatment Options

NICE guidelines recommend the following first-line palliative chemotherapy treatment options for locally advanced or metastatic oesophago-gastric cancer:[24]

- Doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin
- Triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin.

Clinical Trial Information

Trial	**FIGHT;** NCT03694522, 2017-003507-22; FIGHT: A Phase 2 Randomized, Double-Blind, Controlled Study Evaluating Bemarituzumab (FPA144) and Modified FOLFOX6 in Patients With Previously Untreated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Preceded by Dose-Finding in Phase 1 **Phase II** – Completed

	Location(s): 9 EU countries, UK, USA and other countries **Study completion date:** May 2022
Trial Design	Randomised, parallel assignment, double-blinded, placebo controlled
Population	N = 155 (actual); aged 18 years and older; subjects with previously untreated, unresectable, locally advanced or metastatic (not amenable to curative therapy) histologically documented gastric or gastroesophageal junction adenocarcinoma with FGFR2b overexpression
Intervention(s)	Bemarituzumab (IV) 15mg/kg every 2 weeks + single additional bemarituzumab 7.5 mg/kg dose on cycle 1 day 8 + mFOLFOX6 (IV) every 2 weeks
Comparator(s)	Placebo (IV) + mFOLFOX6 (IV) every 2 weeks
Outcome(s)	Progression-Free Survival (PFS) [Time frame: From randomisation until the primary analysis data cut-off date of 23 September 2020]
Results (efficacy)	The primary endpoint was met with an improvement in median PFS of 9.5 months (bemarituzumab) vs 7.4 months (placebo) (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; p=0.07). The secondary endpoint of overall survival (OS) was met; median not reached in the bemarituzumab arm vs 12.9 months for placebo (HR, 0.58, 95% CI, 0.35-0.95; p=0.03). Among patients with measurable disease, overall response rate (ORR) improved from 40% (placebo) to 53% (bemarituzumab). Improved efficacy was observed across all three endpoints (PFS, OS, ORR) with increasing levels of overexpression of FGFR2b on tumour cells.[25]
Results (safety)	Grade ≥3 adverse events (AE) were reported in 83% of patients in the bemarituzumab arm vs 74% patients in the placebo arm with serious AEs in 32% and 36% respectively. Stomatitis was higher in the bemarituzumab arm (31.6% vs 13.0%) and corneal AEs were more common in the bemarituzumab arm (67% vs 10%). There were no reported AEs of retinal detachment or hyperphosphatemia in the bemarituzumab arm.[25]

Clinical Trial Information	
`Trial	**FORTITUDE-101;** NCT05052801, 2023-505457-40; A Randomised, Multi-center, Double-blind, Placebo-controlled Phase 3 Study of Bemarituzumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Subjects With Previously Untreated Advanced Gastric or Gastroesophageal Junction Cancer With FGFR2b Overexpression **Phase III** – Recruiting **Location(s)** – 17 EU countries, USA, Canada and other countries **Primary completion date:** August 2025
Trial Design	Randomised, parallel assignment, double masking, placebo controlled
Population	N = 516 (estimated); aged 18 to 100 years; adults with histologically documented unresectable, locally advanced or metastatic gastric or gastroesophageal junction

	cancer not amenable to curative therapy with FGFR2b ≥10% 2+/3+ tumour cell staining
Intervention(s)	Bemarituzumab (IV) + mFOLFOX6 (IV)
Comparator(s)	Placebo + mFOLFOX6 (IV)
Outcome(s)	OS [Time frame: Up to approximately 3.5 years]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of bemarituzumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma (ID4030). Expected June 2024.
- NICE technology appraisal in development. Pembrolizumab with lenvatinib and chemotherapy for untreated advanced gastro-oesophageal junction cancer (ID 11861). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tislelizumab with chemotherapy for untreated unresectable or metastatic gastric or gastro-oesophageal junction cancer (ID6157). Expected publication date to be confirmed.
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010.
- NICE clinical guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.
- NICE quality standard. Oesophago-gastric cancer (QS176). December 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and Gastric (Adult). B11/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. July 2019.[26]
- European Society of Medical Oncology (ESMO). Oesophageal cancer: ESMO clinical practice guidelines. 2016.[27]
- European Society of Medical Oncology (ESMO). Gastric cancer: ESMO clinical practice guidelines. 2016.[28]
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Additional Information

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