Health Technology Briefing
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Zolbetuximab for previously untreated advanced gastric or gastro-oesophageal junction adenocarcinoma

Company/Developer	Astellas Pharma Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26905	NICE ID: 10579	UKPS ID: 663201

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Zolbetuximab is in clinical development for the treatment of previously untreated metastatic or locally advanced unresectable gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJC) that is HER2-negative and CLDN18.2-positive. GC and GEJC are types of cancers that form in the inner lining of the stomach or where the stomach and the oesophagus meet. Advanced unresectable GC is cancer that started in the stomach and has spread to another part of the body and cannot be removed through surgery. CLDN18.2 is a protein found in the glands lining the inside of the stomach, where it helps the gastric cells to stick to each other. In patients with GC or GEJC, CLDN18.2 is much more widespread and is involved in the survival and spread of the cancer cells. CLDN18.2 represents a potential drug target for the treatment GC or GEJC.

Zolbetuximab is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a part of the CLDN18.2 protein in the gastric cancer cells. By attaching to this protein, zolbetuximab blocks the growth of cancer cells, slowing down the spread of the cancer. Zolbetuximab is administered via intravenous (IV) infusion along with standard-of-care medicines for GC or GEJC. If licensed, zolbetuximab will offer a new treatment option for patients with metastatic or locally advanced unresectable GC or GEJC.

Proposed Indication

For the first-line treatment of adults with Claudin (CLDN) 18.2-positive, human epidermal growth factor receptor-2 (HER2) negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (GEJC).[1]

Technology

Description

Zolbetuximab (Claudiximab, IMAB362) is a novel IgG1 monoclonal antibody which binds to claudin-18 splice variant 2 (CLDN18.2) and mediates cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.[2] In healthy tissue CLDN18.2 is found only in the gastric mucosa tight junctions where it helps cells stick together, but in cancerous cells it is often highly expressed on the cell surface which contributes to survival and spread of cancer cells, making it a target for gastric cancer (GC) or gastro-oesophageal junction adenocarcinomas (GEJC).[2,3,4]

Zolbetuximab is in clinical development for locally advanced unresectable or metastatic treatment-naive GC or GEJC that are CLDN18.2-positive and HER2 negative.[1] In the phase III clinical trials (GLOW, NCT03653507; and SPOTLIGHT, NCT03504397), zolbetuximab will be administered via intravenous (IV) infusion as a 800mg/m^2 loading dose followed by 600mg/m^2 every 3 weeks, in combination with standard-of-care chemotherapy drugs.[1,2,5]

Key Innovation

Zolbetuximab is a first-in-class monoclonal antibody that targets CLDN18.2. Epitopes of CLDN18.2, which are mostly inaccessible to intravenous antibodies, can become exposed to targeted monoclonal antibody–binding during malignant cell transformation.[6] Results from phase II studies show that when it was combined with standard-of-care chemotherapeutic treatments for GC (for example, epirubicin, oxaliplatin and capecitabine), it increased progression free survival from 4.8 to 7.9 months and the overall survival from 8.4 months to 13.2, when compared to the standard chemotherapy alone.[7,8]

HER2 overexpression is seen as an important biomarker for the treatment of gastric adenocarcinoma with many treatments being developed to target this. However, studies have reported that that HER2 is only overexpressed in roughly 22 percent of cases, leaving patients who are HER2-negative with limited treatment options.[9] Notably, zolbetuximab demonstrated potential synergistic efficacy with chemotherapy in preclinical studies; Single-agent zolbetuximab also demonstrated anticancer effects in patients with CLDN18.2-positive advanced GC and GEJC in a phase II study.[6]

If licensed, zolbetuximab will offer a new treatment option for patients with advanced and inoperable gastric or GEJC who are HER2-negative and CLDN18.2-positive.

Regulatory & Development Status

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

Zolbetuximab was granted orphan designation in the EU in November 2010 for the treatment of GC expressing CLDN18.2.[4]

Zolbetuximab is also in phase II clinical development for pancreatic cancer.[10]

Patient Group

Disease Area and Clinical Need

Stomach or GC can start anywhere within the stomach or its walls, the most common form being adenocarcinomas that begin in the glands of the inner stomach lining.[11] GEJC starts where the oesophagus joins the stomach. It is considered GEJC if the centre of the cancer is less than 5cm above or below this junction, but outside of those boundaries it is treated as either stomach or oesophageal cancer. There are three different types of GEJC: Type 1 is the most similar to oesophageal cancer and has spread down into the gastro-oesophageal junction from above; Type 2 is centred at the actual junction; and Type 3, being most similar to GC, has spread up into the junction from below.[12] Over half of GC and GEJC are deemed preventable (54% and 59% respectively), with lifestyle factors such as smoking, alcohol and obesity contributing to the risk, linking incidence rates with deprivation. Prevalence is highest in men and most often seen in those aged 85-90 (2016-18).[13] GC or GEJC can also be linked to certain medical conditions such as gastro-oesophageal reflux disease, long-term helicobacter pylori infection, Barrett's oesophagus, or gastritis, with genetic factors also influencing development risk.[14,15] Exposure to various occupational chemicals can increase the risk of developing GC, such as those found in rubber production plants.[16] Symptoms of gastro-oesophageal cancers can include difficulty and pain when swallowing, nausea or vomiting, heartburn, indigestion, loss of appetite, fatigue, unexplained weight loss, or a lump in the upper abdomen.[17,18]

GEJC is staged according to either oesophagus or GC guidelines depending on how far the centre of the cancer is into the stomach, but most commonly is referred to as GC in literature and statistics.[12,19] GC is the 17th most common cancer in the UK, accounting for 3% of all cancer deaths (2018).[13] Each year in the UK there are approximately 6,453 new cases of GC (2016-18), and the five-year survival rate in England is 21.6% (2013-17).[13] In England (2020-21), there were 6,328 finished consultant episodes (FCE) for malignant neoplasms of the stomach (ICD-10 code: C16.9), with 4,754 hospital admissions that resulted in 12,839 FCE bed days and 3,319 day cases.[20] For malignant neoplasms of the lower third of the oesophagus (GEJC) (ICD-10 code: 15.5) in England (2020-21), there were 19,522 FCE, with 15,925 hospital admissions that resulted in 31,158 bed days and 11,925 day cases.[20]

Recommended Treatment Options

Locally advanced unresectable or metastatic GC and GEJC are ineligible for surgery and therefore can only receive palliative chemotherapy regimens.[21]

NICE guidelines recommend the following chemotherapy treatment options for locally advanced or metastatic oesophago-gastric adenocarcinoma:[22]

- 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.
- Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is recommended as an option for untreated locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative GEJC in adults whose tumours express PD-L1. This is not recommended for GC.

Clinical Trial Information

Trial	**GLOW;** NCT03653507, 2018-000519-26; A Phase 3, Global, Multi-Centre, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus CAPOX Compared With Placebo Plus CAPOX as First-line Treatment of Subjects With Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma **Phase III** – Recruiting **Location(s):** 8 EU countries, UK, USA, Canada and other countries **Primary completion date:** September 2022
Trial Design	Randomised, parallel assignment, double-blind
Population	N= 500 (estimated); Subjects with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma with negative HER2 presentation and >75% positive CLDN18.2 expression; aged 18 years and older
Intervention(s)	Zolbetuximab (IV) + oxaplatin (IV) + capecitabine (oral twice daily)
Comparator(s)	Matched placebo (IV) + oxaliplatin (IV) + capecitabine (oral twice daily)
Outcome(s)	Primary outcome measure: Progression Free Survival (PFS) [Time frame: up to 13 months] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**FAST;** NCT01630083, 2011-005285-38; A Randomized Phase II Multicenter, Open-Label Study Evaluating the Efficacy and Safety of IMAB362 in Combination With the EOX (Epirubicin, Oxaliplatin, Capecitabine) Regimen as First-Line Treatment of Patients With CLDN18.2-Positive Advanced Adenocarcinomas of the Stomach, the Oesophagus or the Gastroesophageal Junction **Phase II** – Completed **Location(s):** 4 EU countries, Ukraine and Russia **Study Completion date:** January 2019
Trial Design	Randomised, parallel assignment, open-label
Population	N= 252; Subjects with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma with positive CLDN18.2; aged 18 years and older
Intervention(s)	Arm 1: + EOX (epirubicin + oxaplatin (IV), capecitabine [oral twice daily]) Arm 2: Zolbetuximab (IV) + EOX (800mg/m^2 then 600mg/m^2) Arm 3: Zolbetuximab + EOX (1000mg/m^2)
Comparator(s)	Epirubicin (IV) + oxaliplatin (IV) + capecitabine (oral twice daily)

Outcome(s)	Primary outcome measures: • Progression Free Survival (PFS) [Time frame: from randomization to the data cut-off date of 31 Jan 2019; maximum time on follow-up was, 68.2, 47.2 & 59.6 months in the EOX, EOX+Zolbetuximab 600 mg, and EOX+Zolbetuximab 1000 mg treatment groups respectively] • Number of Participants with Adverse Events (AEs) [Time frame: from the first dose of study drug administration up to 30 days after the last study medication administration (up to 1,791 days)] See trial record for full list of all outcomes
Results (efficacy)	In the overall population, both PFS [hazard ratio (HR) = 0.44; 95% confidence interval (CI), 0.29-0.67; P < 0.0005] and OS (HR = 0.55; 95% CI, 0.39-0.77; P < 0.0005) were significantly improved with zolbetuximab + EOX (arm 2) compared with EOX alone (arm 1). This significant PFS benefit was retained in patients with moderate-to-strong CLDN18.2 expression in ≥70% of tumour cells (HR = 0.38; 95% CI, 0.23-0.62; P < 0.0005). Significant improvement in PFS was also reported in the overall population of arm 3 versus arm 1 (HR = 0.58; 95% CI, 0.39-0.85; P = 0.0114) but not in high CLDN18.2-expressing patients; no significant improvement in OS was observed in either population.[23]
Results (safety)	Most adverse events (AEs) related to zolbetuximab + EOX (nausea, vomiting, neutropenia, anaemia) were grade 1-2. Grade ≥3 AEs showed no substantial increases overall (zolbetuximab + EOX versus EOX alone). Zolbetuximab + EOX was generally tolerated, and AEs were manageable.[23]

Trial	**SPOTLIGHT;** NCT03504397, 2017-002567-17; A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared With Placebo Plus mFOLFOX6 as First-line Treatment of Subjects With Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma **Phase III -** Recruiting **Location(s):** 6 EU countries, UK, USA, Canada, and other countries **Primary completion date:** February 2022
Trial Design	Randomised, parallel assignment, double-blind
Population	N= 550 (estimated); Subjects with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma with positive CLDN18.2 and HER2-negative expression; aged 18 years and older
Intervention(s)	Zolbetuximab (IV) + mFOLFOX6 (oxaliplatin + folinic acid + fluorouracil) (IV)

Comparator(s)	Placebo (IV) + mFOLFOX6 (IV)
Outcome(s)	Primary outcome measure: Progression Free Survival (PFS) [Time frame: up to 13 months] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of Zolbetuximab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). October 2021
- NICE guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Intrathecal Drug Delivery for Cancer Pain. 2015. D08/P/b.
- NHS England. 2013/14 NHS Standard Contact for Cancer: Oesophageal and Gastric (Adult). B11/S/a/.
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Other Guidance

- European Society of Medical Oncology (ESMO). Oesophageal cancer: ESMO clinical practice guidelines. 2016.[24]
- European Society of Medical Oncology (ESMO). Gastric cancer: ESMO clinical practice guidelines. 2016.[25]
- London Cancer Alliance. LCA oesophageal and gastric cancer clinical guidelines. 2014.[26]
- British Society of Gastroenterology. Guidelines for the management of oesophageal and gastric cancer. 2011.[27]

Additional Information

This technology will require a companion diagnostics test to assess the expression levels of claudin-18.2 (CLDN18.2) in gastro-oesophageal and gastric tumours.[1]

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