Health Technology Briefing
April 2024

Zolbetuximab with nab-paclitaxel and gemcitabine for previously untreated metastatic CLDN18.2-positive pancreatic adenocarcinoma

Company/Developer	Astellas Pharma Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27353	NICE ID: Not available	UKPS ID: 668354

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Zolbetuximab in combination with nab-paclitaxel and gemcitabine is in clinical development for the treatment of Claudin (CLDN) 18.2 positive metastatic pancreatic adenocarcinoma. Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas, a large gland that is part of the digestive system. Metastatic cancer refers to a cancer where the disease has spread from where it first started to another area of the body. Metastatic pancreatic adenocarcinoma develops from cells lining small tubes in the pancreas called ducts. These carry the digestive juices into the main pancreatic duct and then on into the first part of the small intestine. CLDN18.2 a protein that is not expressed in healthy pancreatic tissue but is expressed in 60-90% of pancreatic ductal adenocarcinomas. CLDN18.2 represents a potential target for the treatment of pancreatic adenocarcinomas.

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 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 infusion in combination with nab-paclitaxel and gemcitabine. If licensed, zolbetuximab will offer a new treatment option for patients with CLDN18.2 positive metastatic pancreatic adenocarcinoma.

Proposed Indication

First line treatment of adult patients with Claudin (CLDN) 18.2-positive metastatic pancreatic adenocarcinoma.[1]

Technology

Description

Zolbetuximab (Vyloy, IMAB362) is a novel IgG1 monoclonal antibody which binds to CLDN18.2 and mediates cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.[2] CLDN18.2 is not expressed in healthy pancreatic tissue but is highly activated during carcinogenesis, making it an attractive therapeutic target for treatment of pancreatic adenocarcinoma.[3]

Zolbetuximab in combination with nab-paclitaxel and gemcitabine is in clinical development for the treatment of adult patients with CLDN18.2 positive metastatic pancreatic adenocarcinoma. In phase II clinical trial NCT03816163, zolbetuximab in combination with nab-paclitaxel and gemcitabine will be administered by intravenous (IV) infusion at a dose determined by the Safety Lead-in Phase of the study [1]

Key Innovation

Pancreatic cancer is a difficult-to-treat malignancy with dismal survival outcomes.[4] CLDN18.2 is a protein specifically expressed in the gastric mucosa and is expressed not only in pancreatic cystic tumors (e.g., mucinous cystic tumors and intraductal papillary mucinous neoplasms) but also in 60–90% of pancreatic ductal adenocarcinomas.[3] Zolbetuximab is a selective monoclonal antibody that binds to malignant tissues that highly express CLDN18.2 without affecting healthy tissues that do not express CLDN18.2. This unique cancer-specific feature of zolbetuximab allows for maximum anticancer effects and lower toxicity.[3] If licensed, zolbetuximab in combination with nab-paclitaxel and gemcitabine will offer an additional treatment option for first-line treatment of patients with CLDN18.2 positive metastatic pancreatic adenocarcinoma, who currently have few effective therapies available.

Regulatory & Development Status

Zolbetuximab does not currently have marketing authorisation in the EU/UK for any indication.

Zolbetuximab is in phase III/II clinical development for treatment of other gastrointestinal cancers.[5]

Patient Group

Disease Area and Clinical Need

Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas, a large gland that is part of the digestive system.[6] The most common type of pancreatic cancer (accounting for 95% of cases) is pancreatic ductal adenocarcinoma which develops from ducts (exocrine glands) in the pancreas that carry digestive juices containing enzymes into the main pancreatic duct and then on into the duodenum – the first part of the small intestine which is involved in the chemical digestion of food.[7] Metastatic cancer refers to a cancer where the disease has spread from where it first started to another area of the body. Pancreatic cancer often spreads to the liver, abdominal wall, lungs bones or faraway lymph nodes.[8] CLDN18.2 is a member of the claudin family that is specifically expressed in the gastric mucosa. CLDN18.2 is aberrantly expressed in 60–90% of pancreatic ductal adenocarcinomas.[3] The

majority of cases are sporadic with no known genetic predisposition. Tobacco smoking, alcohol and obesity are known modifiable risk factors. Studies have suggested that approximately 36% of pancreatic cancers in men and 39% in women are linked to lifestyle factors. A hereditary component has been identified in approximately 10% of pancreatic adenocarcinoma cases with a specific germline mutation being implicated in 20% of those cases.[9] Symptoms of pancreatic cancer include: abdomen or back pain, weight loss, jaundice (yellowing of the skin, eyes or both) with or without itching, loss of appetite, nausea, change in stool, pancreatitis and recent-onset diabetes.[8]

In England, in 2022-2023, there were 46,385 finished consultant episodes (FCEs) for malignant neoplasm of the pancreas (ICD-10 code C25) and 37,919 admissions resulting in 88,503 FCE bed days and 30,151 day cases.[10] Furthermore, there were 4,548 deaths with malignant neoplasm of pancreas recorded as the underlying cause in England and Wales in 2022.[11] The age-standardised 1-year and 5-year survival for persons diagnosed pancreatic cancer in England in 2017 was 25.4% and 7.3% respectively.[12]

Recommended Treatment Options

NICE recommends the following treatment for untreated metastatic pancreatic cancer:

- FOLFIRINOX to people with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.[13]
- Nab-paclitaxel (this is paclitaxel as albumin-bound nanoparticles) with gemcitabine if other combination therapies are unsuitable.[14]
- Gemcitabine combination therapy for people who are not well enough to tolerate combination chemotherapy.[13]

Clinical Trial Information

Trial	NCT03816163, EudraCT 2018-002551-15; A Phase 2, Open-Label, Randomized Study to Assess the Efficacy and Safety of Zolbetuximab (IMAB362) in Combination With Nab-Paclitaxel and Gemcitabine (Nab-P + GEM) as First Line Treatment in Subjects With Claudin 18.2 (CLDN18.2) Positive, Metastatic Pancreatic Adenocarcinoma **Phase II –** Recruiting **Location(s):** 4 EU countries, USA and other countries **Primary completion date:** September 2024
Trial Design	Randomised, parallel assignment, open-label
Population	N=369 (estimated); subjects with CLDN18.2 positive PDAC that has not previously been treated with chemotherapy, aged 18 years and older.
Intervention(s)	Participants will be treated with IV zolbetuximab in combination with nab-paclitaxel and gemcitabine, both administered by IV infusion.
Comparator(s)	Participants will be treated with nab-paclitaxel and gemcitabine, both administered by IV infusion.
Outcome(s)	Primary outcome measures: • Dose limiting toxicities - (safety lead in) [time frame: up to 28 days] • Overall survival [time frame: up to 65 months] • Safety assessed by adverse events (AEs) [time frame: up to 65 months] • Safety assessed by incidence of serious adverse events [time frame: up to 65 months]

	• Safety assessed by incidence of treatment emergent adverse events [time frame: up to 65 months] • Number of participants with laboratory value abnormalities and/or AEs [time frame: up to 65 months] • Number of participants with vital sign abnormalities and /or AEs [time frame: up to 65 months] • Number of participants with electrocardiograms abnormalities and or adverse events [time frame: Up to 65 months] • Number of participants with ECOG performance status abnormalities and or adverse events [time frame: Up to 65 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of zolbetuximab is not yet known.

The cost of nab-paclitaxel is £246 for a 100mg vial.[15]

The cost of gemcitabine ranges from £14 per 200mg vial to £385.14 for a 2g/52.6ml vial (38mg/ml).[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer (TA476). September 2017.
- NICE guideline. Pancreatic cancer in adults: diagnosis and management (NG85). February 2018.

NHS England (Policy/Commissioning) 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 Hepatobiliary and Pancreas (Adult). A02/S/a.

Other Guidance

- Journal of the National Comprehensive Cancer Network. Pancreatic Adenocarcinoma Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. 2021.[17]
- European Society for Medical Oncology. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. 2023.[18]

Additional Information

References

1 ClinicalTrials.gov. *A Study to Assess the Efficacy and Safety of IMAB362 in Combination With Nab-Paclitaxel and Gemcitabine (Nab-P + GEM) as First Line Treatment in Subjects With Claudin 18.2 (CLDN18.2) Positive, Metastatic Pancreatic Adenocarcinoma*. *Trial ID: NCT03816163*. 2019. Status: Recruiting. Available from: https://clinicaltrials.gov/study/NCT03816163 [Accessed 21 February 2024].

2 Shah M, Ajani JA, Al-Batran SE, Bang YJ, Catenacci DV, Enzinger P, et al. 836TiP - GLOW: Randomized phase III study of zolbetuximab + CAPOX compared with placebo + CAPOX as first-line treatment of patients with CLD18.2+/HER2− locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. *Annals of Oncology*. 2019;30:v322. https://www.annalsofoncology.org/article/S0923-7534(19)59051-2/fulltext.

3 Park S, Shin K, Kim I-H, Hong T, Kim Y, Suh J, Lee M. Clinicopathological Features and Prognosis of Resected Pancreatic Ductal Adenocarcinoma Patients with Claudin-18 Overexpression. *Journal of Clinical Medicine*. 2023;12(16):5394. https://www.mdpi.com/2077-0383/12/16/5394.

4 Clarivate. *Pancreatic Cancer – Unmet Need – Detailed, Expanded Analysis (US/EU)*. 2021. Available from: https://clarivate.com/products/research-reports/report/unneon0012-2021-biopharma-pancreatic-cancer-unmet-need-detailed/#:~:text=Pancreatic%20cancer%20is%20a%20difficult-to-treat%20malignancy%2C%20with%20dismal,highlighting%20the%20substantial%20unmet%20need%20for%20more-effective%20therapies. [Accessed 27 February 2024].

5 ClinicalTrials.gov. *4 Studies found for: zolbetuximab | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Phase 2, 3*. Available from: https://classic.clinicaltrials.gov/ct2/results?term=zolbetuximab&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=&phase=1&phase=2&Search=Apply [Accessed 27 Februaury 2024].

6 National Health Service (NHS). *Pancreatic cancer*. Available from: https://www.nhs.uk/conditions/pancreatic-cancer/ [Accessed 27 February 2024].

7 Pancreatic Cancer UK. *Types of pancreatic cancer*. 2022. Available from: https://www.pancreaticcancer.org.uk/information/just-diagnosed-with-pancreatic-cancer/pancreatic-ductal-adenocarcinoma-and-other-exocrine-tumours/ [Accessed 27 February 2024].

8 Pancreatic Cancer Action Network. *Advanced Cancer*. Available from: https://www.pancan.org/facing-pancreatic-cancer/living-with-pancreatic-cancer/advanced-cancer/ [Accessed 27 Februaury 2024].

9 Becker AE, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. *World journal of gastroenterology*. 2014;20(32):11182-98. Available from: https://doi.org/10.3748/wjg.v20.i32.11182.

10 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-23: Diagnosis*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 14 December 2023].

11 Office for National Statistics. *Deaths registered in England and Wales, 2022*. 2023. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables [Downloaded 27 February 2024].

12 Office for National Statistics. *Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsfollowedupto2018 [Downloaded 26 February 2024].

13 National Institute for Health and Care Excellence (NICE). *Pancreatic cancer in adults: diagnosis and management* (*NG85)*. Available from: https://www.nice.org.uk/guidance/ng85/chapter/Recommendations#managing-unresectable-pancreatic-cancer [Accessed 27 Februaury 2024].

14 National Institute for Health and Care Excellence (NICE). *Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer* (*TA476)*. Available from: https://www.nice.org.uk/guidance/ta476 [Accessed 27 Februaury 2024].

15 National Institute for Health and Care Excellence (NICE). *Paclitaxel [Specialist drug] - Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/paclitaxel-specialist-drug/medicinal-forms/ [Accessed 15 April 2024].

16 British National Formulary (BNF). *Gemcitabine [Specialist drug] Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/gemcitabine-specialist-drug/medicinal-forms/ [Accessed 22 Februaury 2024].

17 Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2021;19(4):439-57. Available from: https://doi.org/10.6004/jnccn.2021.0017.

18 Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]. *Annals of Oncology*. 2023;34(11):987-1002. Available from: https://doi.org/10.1016/j.annonc.2023.08.009.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.