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Health Technology Briefing
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Zanidatamab for treating advanced or metastatic HER2-positive biliary tract cancer in adults

Company/Developer	Jazz Pharmaceuticals UK Limited

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30259	NICE TSID: Not available	UKPS ID: 669665

Licensing and Market Availability Plans

Currently in phase II clinical trials

Summary

Zanidatamab is being developed for adult patients with advanced or metastatic human epidermal growth factor-2 (HER2)-positive biliary tract cancer (BTC). BTCs are a rare and diverse group of aggressive cancers arising from the gallbladder and bile ducts. The bile ducts are tubes that link the gallbladder, liver, and pancreas together, all of which are used in digestion. HER2 is linked to increased tumour growth when found in high levels on cancer cells. Surgical management can be curative in early-stage BTC; however, relapse rates (when the cancer comes back) are high. A high proportion of patients have advanced or metastatic disease which means the cancer has spread around the body at diagnosis and are currently managed with palliative chemotherapy or supportive care. BTC is associated with a poor prognosis. Currently, there is a lack of effective therapeutic options for patients with advanced or metastatic BTC. There is a need for alternative treatments such as biological therapies.

Zanidatamab is a medicinal product designed to increase antitumor activity in patients by attaching to HER2 which is on the surface of the cancer cells, helping them to be destroyed by the body's immune system. Zanidatamab is administered intravenously (IV). If licensed, Zanidatamab will offer the first second line treatment option for advanced HER2-positive BTC.

Proposed Indication

For the treatment of adult patients with human epidermal growth factor receptor 2-positive (HER2-positive) locally advanced (unresectable) or metastatic biliary tract cancer (BTC) who have progressed after at least one prior line of systemic therapy.[1]

Technology

Description

Zanidatamab (ZW25; JZP598)[2] is a novel, bispecific antibody that simultaneously binds two distinct sites on HER2. This binding results in multiple mechanisms of action of zanidatamab, which leads to improved binding, clustering, and receptor internalisation and HER2 downregulation, inhibition of ligand dependent and independent proliferation, and potent activation of antibody dependent cellular cytotoxicity.[3] Some patients with BTC produce large quantities of HER2 protein on their cell surface and this plays a role in tumour growth. By attaching to HER2, zanidatamab inhibits the HER2 growth signal pathway and reduces uncontrolled cell proliferation of these cancer cells. zanidatamab also activates cells of the immune system, which then kill the cancer cells These actions are expected to slow down the progress of the disease. [4]

Zanidatamab is in development for the treatment of patients with advanced or metastatic HER2-positive BTC who have had one or more prior therapies. In the phase II clinical trial (NCT04466891), patients were administered with zanidatamab 20 mg/kg intravenously (IV) every 2 weeks until disease progression, unacceptable toxicity or withdrawal of consent.[5]

Key Innovation

Advanced, unresectable BTC are aggressive in nature with limited treatment options, and poor prognosis. Chemotherapy is the mainstay of the current treatment, which results in a median overall survival of less than one year, underscoring the need for novel therapeutic agents and strategies.[6] Zanidatamab is well tolerated and has an encouraging single-agent activity, both in terms of response rate and duration of response, in pre-treated patients with advanced HER2-positive BTC. Zanidatamab demonstrated meaningful clinical benefit with a manageable safety profile as a second-line treatment for HER2-positive advanced or metastatic BTC. If licensed, zanidatamab, will offer the first targeted therapy option for BTC patients who have received at least one prior therapy, expanding the precision medicine options.[6,7]

Regulatory & Development Status

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

Zanidatamab is currently in clinical development as combination and monotherapy for HER2-expressing cancers including: [8]

- Gastric cancer
- Breast cancer
- Oesophageal cancer
- Colorectal cancer

Zanidatamab has the following regulatory designations: [9,10]

- An orphan drug in the EU in July 2021 for the treatment of BTC
- A Breakthrough Therapy by the US FDA for the treatment of patients with HER2 gene–positive BTC who have either received prior systemic chemotherapy for locally advanced (unresectable) or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant systemic chemotherapy in November 2020

Patient Group

Disease Area and Clinical Need

BTC refers to a type of carcinoma affecting the biliary system, which includes both the gallbladder and the bile ducts. BTCs are a group of rare and aggressive malignancies which arise from the gallbladder (gallbladder cancer, GBC), intrahepatic or extrahepatic bile ducts (cholangiocarcinoma, iCCA or eCCA), or ampulla of Vater (ampullary cancer).[11] Patients with BTC often experience symptoms from both systemic and local consequences of disease. Frequently reported symptoms include jaundice, abdominal pain, pruritus, nausea, unintentional weight loss, fever, and fatigue.[5,12] It is not always clear what causes BTC but risk factors include being over the age of 65 years and having certain medical conditions such as abnormal bile ducts, ulcerative colitis, liver flukes, bile duct stones, or liver cirrhosis.[13]

In England (2022-23), there were 13,240 finished consultant episodes (FCE) and 9,911 admissions for BTC (ICD10 C22.1, C24.0, C24.8, C24.9), resulting in 38,521 FCE bed days and 7,061 day cases.[14] Approximately 5-20% of the total number of FCEs and admissions are HER2-positive.[15] BTC is associated with high mortality. BTCs have a mortality rate of 3.64 per 100,000 population in England.[16] There are no UK wide statistics available for biliary tract cancer survival. However, regarding the 1-year survival rate for those diagnosed with BTC in England in 2012, almost 30% of men and 25% of women survived their cancer for 1 year or more after being diagnosed. In regard to 5-year survival rate in 2008, more than 5% of men and almost 5% of women survived their cancer for 5 years or more after they were diagnosed.[17]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatments for advanced or metastatic BTC. Treatment depends on size, type of BTC and if the cancer has spread. If it is not possible to cure the cancer then chemotherapy or radiotherapy may be given to control the growth and help with symptoms, with FOLFOX deemed standard of care for chemotherapy in patients who have received at least one prior therapy.[18]

Clinical Trial Information

Trial	NCT04466891, 2020-000459-11; A Phase 2b, Open-label, Single-arm Study of ZW25 Monotherapy in Subjects with Advanced or Metastatic HER2-positive Biliary Tract Cancers **Phase II** – Active, not recruiting **Location(s):** Three EU countries, UK, USA, Canada, and other countries **Primary completion date:** July 2023
Trial Design	Single group assignment, open label
Population	N= 80 (actual) subjects with HER2-amplified, inoperable and advanced or metastatic BTC, including ICC, ECC, and GBC, who received at least 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, and experienced disease progression after or developed intolerance to the most recent prior therapy

Intervention(s)	Zanidatamab IV infusion 20 mg/kg every 2 weeks until unacceptable toxicity or disease progression.[3]
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measures: - Confirmed objective response rate (ORR) by independent central review (ICR) [Time Frame: Up to 2.5 years] See trial record for full list of other outcomes.
Results (efficacy)	Confirmed objective responses by independent central review were observed in 33 patients in cohort 1 (41.3% [95% CI 30.4–52.8]).[5]
Results (safety)	The most common treatment-related adverse events occurring in >10% of patients; the most common were diarrhoea (four [5%] patients) and decreased ejection fraction (three [3%] patients). There were no grade 4 treatment-related adverse events and no treatment-related deaths.[5]

Estimated Cost

The cost of zanidatamab is not yet known.

Relevant Guidance

NICE Guidance

- NICE interventional procedures guidance. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (IPG630). October 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma (16022/P). July 2016.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- European Society for Medical Oncology. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. February 2023.[19]
- British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. August 2012.[20]

Additional Information

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