

Health Technology Briefing November 2021

Pembrolizumab in combination with gemcitabine and cisplatin for previously untreated advanced/unresectable biliary tract cancer

Company/Developer

Merck Sharp & Dohme Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 28138

NICE ID: 10464

UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Pembrolizumab in combination with gemcitabine plus cisplatin is being developed for patients with advanced/unresectable biliary tract cancer (BTC). BTC is a rare type of cancer that affects bile ducts and the gallbladder. Bile ducts are tubes that connect the gallbladder and liver to the small bowel. Bile is produced in the liver and stored in the gallbladder where it is transported to the small intestine to aid the digestion of fatty foods. Advanced biliary tract cancer is cancer that has grown a considerable amount and/or spread to other areas of the body and is incurable. Unresectable BTC is cancer that cannot be surgically removed. Chemotherapy using gemcitabine and cisplatin is standard of care for first-line therapy in patients whose cancer is inoperable, but the disease has a poor outcome. There is a need for alternative treatments such as biological therapies.

Pembrolizumab is a type of protein (monoclonal antibody) that has been designed to increase the immune system's ability to kill cancer cells. Pembrolizumab is mainly used in adults for cancers that are advanced, have spread to other parts of the body (metastatic) or are not responding to other treatments. Pembrolizumab is administered with gemcitabine and cisplatin intravenously. If licensed, pembrolizumab will offer an additional treatment option for adults with advanced/unresectable BTC.

Proposed Indication

First line treatment of adult patients with advanced/unresectable biliary tract carcinoma (BTC).¹

Technology

Description

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.^{2,3}

Pembrolizumab in addition to cisplatin and gemcitabine is currently in phase III clinical development for the treatment of adult patients with advanced and/or unresectable biliary tract carcinoma (BTC). In the phase III clinical trial (KEYNOTE-966; NCT04003636), 200 mg of pembrolizumab is administered intravenously once every 3 weeks for up to 35 cycles in addition to gemcitabine and cisplatin.¹

Key Innovation

Currently, approved therapies for advanced and/or unresectable BTC include radiotherapy and chemotherapy.^{4,5} BTCs express PD-L1 and high levels of soluble PD-L1 correlate with poor prognosis in BTC patients treated with chemotherapy.⁶ Most patients present with advanced or unresectable disease on diagnosis, for which the current standard of care is gemcitabine plus cisplatin. Median survival for these patients is only 12 months, highlighting the need for more effective therapies. Pembrolizumab is a PD-1 inhibitor that has demonstrated modest antitumor activity as monotherapy in patients with previously treated BTC and has improved survival when used in combination with platinum-based chemotherapy in other cancer types.⁷ In addition, pembrolizumab is mainly used in adults for cancers that are advanced, have spread to other parts of the body or are not responding to other treatments.⁸

If approved, pembrolizumab in addition to cisplatin and gemcitabine would provide a new first-line treatment option for adults with advanced and/or unresectable BTC.

Regulatory & Development Status

Pembrolizumab as a monotherapy or in combination with various medicinal products is currently licensed in the UK for the following indications:^{2,9}

- Melanoma
- Non-small cell lung carcinoma (NSCLC)
- Classical Hodgkin lymphoma (cHL)
- Urothelial carcinoma
- Head and neck squamous cell carcinoma (HNSCC)
- Renal cell carcinoma (RCC)
- Colorectal cancer (CRC)
- Oesophageal carcinoma
- Triple-negative breast cancer

Pembrolizumab is currently in phase II/III clinical development for the treatment of various types of cancer some of which include:¹⁰

- Nasopharyngeal Carcinoma
- Locally Advanced Adenocarcinoma of Esophagogastric Junction
- Thymic Carcinomas
- Muscle-Invasive Bladder Cancer
- Non-small-cell Lung Cancers
- Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Pembrolizumab was granted orphan drug designation in the USA in 2015 for the treatment of gastric cancer, including gastroesophageal junction adenocarcinoma.¹¹

Patient Group

Disease Area and Clinical Need

Biliary tract carcinoma (BTC) is a type of cancer that affects the biliary system, which includes the bile ducts and gallbladder. Bile ducts are small tubes that connect the liver and gallbladder to the small intestine and produce bile to help break down fats in food.^{12,13} The gallbladder is a small, pear-shaped pouch in the upper abdomen that stores bile, which is made in the liver. Cancer that develops in the bile ducts is termed cholangiocarcinoma (CCA) which is categorised based on the part of the bile duct from which it develops. Intrahepatic CCA originates in the bile ducts within the liver and accounts for 10%–20% of CCA cases. Hilar CCA originates just outside the liver, where the left and right hepatic ducts join together and are the most common type of CCA, accounting for 50% of cases. Extrahepatic CCA originates in bile ducts further away from the liver, including the bile ducts running through the pancreas to the small intestine, and accounts for 30%–40% of CCAs.¹⁴

BTC is relatively uncommon, accounting for less than 1% of all human cancers. It is most commonly diagnosed in people between the ages of 60 and 70 years and affects slightly more men than women.¹⁴ The exact causes of BTC are not known, but certain factors can increase the risk of a person developing this; including having abnormal bile ducts, medical conditions such as primary sclerosing cholangitis, bile duct stones, ulcerative colitis, liver cirrhosis, porcelain gallbladder.¹⁴⁻¹⁶

Advanced cancer occurs when the cancer is not localised anymore to one site and has developed metastasis. Unresectable cancer is defined as a cancer that cannot be removed completely through surgery.¹⁷ BTCs usually present at an advanced stage and are characterised by poor prognosis.⁵ Surgical resection is regarded as the curative treatment option for patients with BTC but most patients are not considered suitable candidates for surgery because of an advanced disease status at diagnosis.¹⁸ Symptoms of BTC vary depending on where the cancer is located in the biliary tract. Some of these symptoms include:¹⁴

- Weight loss
- Jaundice
- Stomach pain
- Excessively dark urine and pale stools
- Fever

The incidence rate of BTC in England is 3.58 per 100,000; applying this estimate to the mid-year 2020 population for England would equal approximately 2,398 people affected by this condition. In England, in 2020-21, there were 11,080 finished consultant episodes (FCE) and 7,960 admissions for BTC (ICD10 C22.1, C24.0, C24.8, C24.9).^{19,20} BTCs have a mortality rate of 3.64 per 100,000 population in England.²¹

Currently, there are no UK wide statistics available for bile duct cancer and gallbladder cancer survival by stage.^{22,23}

Recommended Treatment Options

Treatments for BTC are discussed between the patient and a multidisciplinary team that includes healthcare professionals and experts, in order to help identify the most suitable option for the patient depending on their preference, disease progression and location.¹³

Chemotherapy is typically used in the first-line treatment of BTC that cannot be surgically removed. Patients with unresectable BTC and who are in good general health, are typically offered chemotherapy with a combination of cisplatin and gemcitabine. In some patients, oxaliplatin might be given instead of cisplatin, especially if there are any concerns over kidney function. Patients with poorer overall health might be offered single-agent chemotherapy with gemcitabine, fluorouracil (5-FU) or capecitabine alone. Patients who experience cancer progression following first-line treatment can be offered further chemotherapy.

Radiotherapy is not commonly used in the treatment of unresectable BTC but may be considered for some patients to relieve some symptoms.¹⁴

Clinical Trial Information

Trial	KEYNOTE-966; NCT04003636; 2019-000944-82 ; A Phase 3 Randomised, Double Blind Study of Pembrolizumab Plus Gemcitabine/Cisplatin Versus Placebo Plus Gemcitabine/Cisplatin as First-Line Therapy in Participants With Advanced and/or Unresectable Biliary Tract Carcinoma Phase III - Active, Not recruiting Location(s): 7 EU countries, UK, USA, Canada and other countries Primary completion date: August 2023
Trial Design	Randomised, parallel assignment, triple-blind
Population	N= 1048; Subjects 18 years and older with a histologically confirmed diagnosis of advanced (metastatic) and/or unresectable (locally advanced) BTC (intra- or extrahepatic cholangiocarcinoma or gallbladder cancer)
Intervention(s)	Pembrolizumab 200 mg (IV) + Gemcitabine 1000 mg/m ² (IV) + Cisplatin 25 mg/m ² (IV) every 3 weeks See trial record for dosage.
Comparator(s)	Matched placebo + gemcitabine + cisplatin
Outcome(s)	Primary outcome measure: Overall Survival (OS) [Time Frame: Up to approximately 41 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100mg/4ml vial costs £2630.²⁴

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Infigratinib for cholangiocarcinoma (TA10882). Expected date of issue to be confirmed.
- NICE interventional procedures guidance. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (IPG630). October 2018.
- NICE interventional procedures guidance. Photodynamic therapy for bile duct cancer (IPG134). July 2005.

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

- NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers, Version 2. May 2021.²⁵
- European Society for Medical Oncology. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2016.²⁶
- Bridgewater J, Galle PR, Khan S, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. June 2014.²⁷
- British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. August 2012.²⁸

Additional Information

References

- 1 Clinical Trials.gov. *Pembrolizumab (MK-3475) Plus Gemcitabine/Cisplatin Versus Placebo Plus Gemcitabine/Cisplatin for First-Line Advanced and/or Unresectable Biliary Tract Carcinoma (BTC) (MK-3475-966/KEYNOTE-966) (KEYNOTE-966)*. Trial ID: NCT04003636. 2019. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT04003636> [Accessed 25 October 2021].
- 2 Electronic Medicines Compendium (eMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. 2021. Available from:

- https://www.medicines.org.uk/emc/product/2498/smpc#PHARMACOLOGICAL_PROPS [Accessed 21 October 2021].
- 3 (NIH) NIOH. *Pembrolizumab*. 2014. Available from: <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/pembrolizumab?redirect=true> [Accessed 21 October 2021].
- 4 National Health Services (NHS). *Treatment -Bile duct cancer (cholangiocarcinoma)*. Available from: <https://www.nhs.uk/conditions/bile-duct-cancer/treatment/> [Accessed 21 October 2021].
- 5 Oneda E, Abu Hilal M, Zaniboni A. Biliary tract cancer: current medical treatment strategies. *Cancers*. 2020;12(5):1237. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7281170/>.
- 6 Oh D-Y, Chen L-T, He A, Okusaka T, Qin S, Chin S, et al. A phase III, randomized, double-blind, placebo-controlled, international study of durvalumab in combination with gemcitabine plus cisplatin for patients with advanced biliary tract cancers: TOPAZ-1. *Annals of Oncology*. 2019;30:v319. Available from: <https://www.sciencedirect.com/science/article/pii/S0923753419590469>.
- 7 Valle JW, Kelley R, Furuse J, Edeline J, Finn R, Ren Z, et al. 78TiP KEYNOTE-966 trial in progress: Pembrolizumab plus gemcitabine and cisplatin for advanced biliary tract cancer. *Annals of Oncology*. 2020;31:S270-S1. Available from: [https://www.annalsofoncology.org/article/S0923-7534\(20\)40052-3/fulltext](https://www.annalsofoncology.org/article/S0923-7534(20)40052-3/fulltext).
- 8 European Medicines Agency (EMA). *Keytruda (pembrolizumab)*. 2021. Available from: https://www.ema.europa.eu/en/documents/overview/keytruda-epar-medicine-overview_en.pdf [Accessed 1 November 2021].
- 9 European Medicines Agency (EMA). *Keytruda*. 2021. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda> [Accessed 9 November 2021].
- 10 Clinical Trials.gov. *Pembrolizumab | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=Pembrolizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 21 October 2021].
- 11 U.S. Food and Drug Administration. *Search Orphan Drug Designations and Approvals*. Available from: <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=481715> [Accessed 1 November 2021].
- 12 National Health Services (NHS). *What is bile duct cancer? -Bile duct cancer (cholangiocarcinoma)*. Available from: <https://www.nhs.uk/conditions/bile-duct-cancer/> [Accessed 25 October 2021].
- 13 Macmillan Cancer Support. *Bile duct cancer (cholangiocarcinoma)*. Available from: <https://www.macmillan.org.uk/cancer-information-and-support/bile-duct-cancer> [Accessed 25 October 2021].
- 14 European Society for Medical Oncology (ESMO). *Biliary tract cancer - An ESMO guide for patients*. 2020. Available from: <https://ammf.org.uk/wp-content/uploads/2020/02/EN-Biliary-Tract-Cancer-Guide-for-Patients.pdf> [Accessed 1 November 2021].
- 15 Cancer Research UK. *What is bile duct cancer?* Available from: <https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/about> [Accessed 25 October 2021].
- 16 The Alan Morement Memorial Fund (AMMF) The Cholangiocarcinoma. *Causes and risk factors - What causes cholangiocarcinoma (bile duct cancer)?* Available from: <https://ammf.org.uk/causes-and-risk-factors/> [Accessed 25 October 2021].
- 17 National Cancer Institute. *Unresectable*. Available from: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/unresectable> [Accessed 1 November 2021].

- 18 Lee SH, Lee HS, Lee SH, Woo SM, Kim DU, Bang S. Efficacy and safety of pembrolizumab for gemcitabine/cisplatin-refractory biliary tract cancer: a multicenter retrospective study. *Journal of clinical medicine*. 2020;9(6):1769. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7355970/>.
- 19 Public Health England. *National Cancer Intelligence Network Rare and less common cancers - Incidence and Mortality in England, 2010 to 2013*. 2015. Available from: https://ammf.org.uk/wp-content/uploads/2015/06/Rare_and_less_common_cancers_For-AMMF-web_0-1.pdf [Accessed 1 November 2021].
- 20 NHS Digital. *Hospital Admitted Patient Care Activity*. 2021. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity> [Accessed 25 October 2021].
- 21 The Alan Morement Memorial Fund (AAMF). *Cholangiocarcinoma mortality higher than incidence?* Available from: <https://ammf.org.uk/2015/06/25/cholangiocarcinoma-mortality-higher-than-incidence/> [Accessed 25 October 2021].
- 22 cancer Research UK. *Survival for bile duct cancer*. Available from: <https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival> [Accessed 1 November 2021].
- 23 Cancer Research UK. *Gallbladder cancer - Survival*. Available from: <https://about-cancer.cancerresearchuk.org/about-cancer/gallbladder-cancer/survival> [Accessed 1 November 2021].
- 24 The National Institute for Health and Care Excellence (NICE) BNF. *Pembrolizumab*. Available from: <https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html> [Accessed 25 October 2021].
- 25 Benson 3rd AB, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, et al. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *Journal of the National Comprehensive Cancer Network: JNCCN*. 2009;7(4):350-91. Available from: <https://pubmed.ncbi.nlm.nih.gov/34030131/>.
- 26 Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2016;27:v28-v37. Available from: [https://www.annalsofoncology.org/article/S0923-7534\(19\)31642-4/fulltext](https://www.annalsofoncology.org/article/S0923-7534(19)31642-4/fulltext).
- 27 Bridgewater J, Galle PR, Khan SA, Llovet JM, Park J-W, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of hepatology*. 2014;60(6):1268-89. Available from: <https://pubmed.ncbi.nlm.nih.gov/24681130/>.
- 28 Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut*. 2012;61(12):1657-69. Available from: <https://gut.bmj.com/content/61/12/1657>.

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