NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
SEPTEMBER 2020

Bintrafusp alfa for locally advanced or metastatic biliary tract cancer – second-line

NIHRIO ID	27808	**NICE ID**	10463
Developer/Company	GlaxoSmithKline UK and Merck KGaA	**UKPS ID**	657313

Licensing and market availability plans	Currently in Phase II clinical trials.

SUMMARY

Biliary tract cancer (BTC) is a rare type of cancer that affects bile ducts, which are tubes that link the gallbladder, liver and pancreas together. Bile is produced in the gallbladder and is transported to the small intestine to aid the digestion of fatty foods. Advanced or metastatic biliary tract cancer is cancer that has grown a considerable amount and/or spread to other areas of the body and is incurable. Chemotherapy using gemcitabine and cisplatin is standard of care for first-line therapy in patients whose cancer is inoperable, and there are very limited second-line therapies for patients who have received platinum-based chemotherapy but where the cancer has not responded or relapsed.

Bintrafusp alfa, delivered via intravenous injection, is a novel bi-functional fusion protein that is composed of an antibody fused with a receptor. Chemotherapy aims to kill cancer cells by directly attacking them, whereas bintrafusp alfa works twofold by preventing cancer from being resistant to a patient's immune system and stopping cancer cells from growing.

PROPOSED INDICATION

Second-line treatment of locally advanced or metastatic BTC for patients who have failed or are intolerant to first-line platinum-based chemotherapy.[a]

TECHNOLOGY

DESCRIPTION

Bintrafusp alfa (M7824; Anti-PD-L1/TGF-beta Trap) is a first-in-class bi-functional fusion protein composed of a monoclonal antibody against programmed death ligand 1 (PD-L1) fused to the extracellular domain of human transforming growth factor- β (TGF- β) receptor II, which functions as a "trap" for all three TGF-β isoforms. This works simultaneously by blocking the PD-L1 and TGF-β pathways.[1,2] This is used to prevent TGF-β-mediated tumour development and metastasis, as well as restoring and enhancing anti-tumour responses by PD-L1 inhibition.[3]

Bintrafusp alfa is currently in Phase II (NCT03833661) development for the treatment of BTC, for patients who have failed or are intolerant to first line platinum-based chemotherapy, at a dose of 1200mg by intravenous injection once every two weeks.[4]

INNOVATION AND/OR ADVANTAGES

At present there are no licenced or recommended treatments for the second-line treatment of BTC in the UK.[5] Although chemotherapy options are available, they offer increased survival but with increased adverse side-effects versus best standard of care (BSC). A recent ABC-06 clinical trial demonstrated that a modified FOLFOX regimen increased 6-month survival by 50.6% and 12-month survival by 25.9%, compared to BSC which was 35.5% and 11.4% respectively. However, there was toxicity associated with this regimen with 59% Grade 3/4 toxicities reported for FOLFOX regimen compared to 39% for BSC.[6] Furthermore, not all patients requiring second-line treatment will be suitable for chemotherapy.

Bintrafusp alfa is a novel biological entity that brings together a TGF-β trap combined with an anti-PD-L1 mechanism in order to simultaneously block the two immunosuppressive pathways.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Bintrafusp alfa does not currently have Marketing Authorisation in the EU for any indication.

Bintrafusp alfa is currently in Phase II development for the following conditions:[8]

- Non-small cell lung cancer
- Triple negative breast neoplasms
- Uterine cervical neoplasms
- Urothelial cancer

[a] Information provided by GlaxoSmithKline UK on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

BTC is a rare type of primary liver cancer that affects the biliary system including 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.[9-12] The biliary system is made up of branch-like ducts called intrahepatic ducts that run throughout the liver and a duct that comes from the gallbladder called a cystic duct, which converge to form the common bile duct (extrahepatic bile duct). The common bile duct is located outside of the liver, behind the pancreas, and transports bile to the small intestine to aid digestion.[9,12]

The exact causes of BTC are not known, but certain factors can increase the risk of a person developing this. These include being over the age of 60 years, having abnormal bile ducts, medical conditions such as primary sclerosing cholangitis, bile duct stones, ulcerative colitis and environmental factors like exposure to thorotrast (a now discontinued contrast agent previously used in X-rays).[13-16]

Advanced cancer occurs when the cancer is not localised anymore to one site and has developed metastasis. Patients with BTC that is locally advanced (also known as regional) means the cancer has developed from its original location but remains in the biliary system, whereas metastatic BTC (also known as distant) has spread from its primary location in the biliary system to other areas of the body.[17,18] Treatment for advanced cancers aims to slow cancer spread, shrink the cancer area, relieve symptoms and increase life years.[17]

The average age of diagnosis is ≥65 years, with older patients at a higher risk of not being suitable for chemotherapy.[19] Symptoms of BTC vary depending on where the cancer is in the bile ducts, however cancer that begins in the liver bile ducts (intrahepatic ducts) is difficult to notice as the liver is a resilient organ. In cases of intrahepatic duct cancer symptoms may not being to show until the cancer is advanced. Symptoms can include:[20-22]

- Jaundice
- Darker urine
- Paler faeces
- Itchy skin
- Loss of appetite
- Unintentional weight loss
- Stomach pain
- Higher temperature and shivering
- Fatigue

CLINICAL NEED AND BURDEN OF DISEASE

In 2017 in England, approximately 2,187 people were diagnosed with intrahepatic bile duct carcinoma (also known as intrahepatic cholangiocarcinoma), a type of BTC (ICD10 C22.1).[23] Due to the rarity and subtypes of the cancer it is difficult to estimate the statistics and individuals may be placed under alternative diagnoses, such as malignant neoplasm of liver and intrahepatic bile ducts (ICD10 C22), and other and unspecific parts of the biliary tract (ICD10 C24).[24] Between 2018-19 in England the number of finished consultant episodes (FCE) for intrahepatic bile duct carcinoma (ICD-10 C22.1) was 9,560 with a total of 31,601 bed days.[25]

There are no UK-wide statistics for BTC survival by stage.[26] However based on US Surveillance, Epidemiology, and End Results (SEER) data from 2000 to 2006 for intrahepatic cholangiocarcinoma,

around 5% of people with regional cancer survived ≥ 5 years after diagnosis, whereas 2% of people with distant cancer survived ≥ 5 years after diagnosis. For extrahepatic cholangiocarcinoma around 25% of people with regional BTC survived ≥ 5 years, whereas 2% of people with distant BTC survived ≥ 5 years after diagnosis.[26] From data in England incidence has increased from 2.7 per 100,000 (2001) to 4.3 per 100,000 (2017), and mortality rates from 2.6 per 100,000 (2001) to 4.7 per 100,000 (2017) of BTC are increasing, particularly for intrahepatic cholangiocarcinoma.[23]

From Public Health England data from 2008 and 2012 for all stages of BTC, women diagnosed in England had a one-year survival rate of 25% (2012) and approximately a five-year survival rate of 5% (2008). On the other hand, men in England diagnosed with BTC had approximately a one-year survival rate of 30% (2012) and a five-year survival rate of 5% (2008).[26]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

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.[10] Radiotherapy is not routinely used to treat BTC, however in some circumstances it can be used to kill cancerous cells and for palliative care to reduce symptoms.[27,28] Chemotherapy is also offered and may be used post-surgery to prevent relapse, to reduce cancer size or alongside radiotherapy in some cases.[10,28] If the BTC becomes advanced patients are assigned to a palliative care or symptom control team to receive chemotherapy treatment that will limit the cancer and symptoms to help increase life years.[28]

CURRENT TREATMENT OPTIONS

First-line treatment for BTC consists of platinum-based chemotherapy, such as a combination of gemcitabine and cisplatin, or combination of capecitabine, fluorouracil and oxaliplatin.[27,29] However, there is no consensus on secondary therapy for patients who have received platinum-based chemotherapy but where the cancer has not responded or relapsed.[5,30]

PLACE OF TECHNOLOGY

If licensed, bintrafusp alfa will offer a second-line treatment for locally advanced or metastatic BTC for patients who have failed or are intolerant to first line platinum-based chemotherapy.[31]

CLINICAL TRIAL INFORMATION

Trial	**NCT03833661; 2018-003707-19; A Phase II, Multicenter, Open-label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or Are Intolerant to First-line Platinum-Based Chemotherapy** **Phase II:** Ongoing **Location(s):** EU (including UK), USA and other countries **Primary completion date:** 9th Nov 2020

Trial design	Single group assignment with open label.
Population	N=159 (actual); adults over 18 years; with histologically or cytologically confirmed locally advanced or metastatic BTC (cholangiocarcinoma and gallbladder cancer); participants must have failed or be intolerant to 1L systemic platinum-based chemotherapy.
Intervention(s)	Bintrafusp alfa (M7824) intravenous infusion of 1200mg every two weeks until confirmed disease progression, death, unacceptable toxicity or study withdrawal.
Comparator(s)	No comparator.
Outcome(s)	Confirmed Objective Response (OR) According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) as Evaluated by Independent Review Committee [Time Frame: Time from first treatment to planned final assessment at approximately 2.5 years]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of bintrafusp alfa is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations (ID3740). Publication date TBC.
- NICE interventional procedures guidance in development. Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma (GID-IPG10067). Publication date TBC.
- NICE interventional procedures guidance. Irreversible electroporation for primary liver cancer (IPG664). November 2019.
- NICE interventional procedures guidance. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (IPG630). October 2018.
- NICE interventional procedures guidance. Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cancer (IPG614). May 2018.
- NICE interventional procedures guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer (IPG488). May 2014.
- NICE interventional procedures guidance. Cryotherapy for the treatment of liver metastases (IPG369). December 2010.
- 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.

OTHER GUIDANCE

- NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers, Version 5. August 2020.[32]
- European Society for Medical Oncology. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2016.[31]
- US Mayo Clinic. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. January 2014.[33]
- British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. August 2012.[34]

ADDITIONAL INFORMATION

REFERENCES

1 Lan Y, Zhang D, Xu C, Hance K, Marelli B, Qi J, et al. Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-β. *Science Translational Medicine*. 2018 Jan;10(424):eaan5488. Available from: https://stm.sciencemag.org/content/10/424/eaan5488.

2 Yoo C, Oh D, Choi H, Kudo M, Kondo S, Chen L, et al. Phase I study of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in patients with pretreated biliary tract cancer *Journal for ImmunoTherapy of Cancer,*. 2020 May;8(e000564). Available from: https://jitc.bmj.com/content/8/1/e000564.

3 Marshall H, Djamgoz M. Immuno-Oncology: Emerging Targets and Combination Therapies. *Frontiers in Oncology*. 2018 Aug;Review article. Available from: https://doi.org/10.3389/fonc.2018.00315.

4 Clinicaltrials.gov. *M7824 Monotherapy in Locally Advanced or Metastatic Second Line (2L) Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer)*. *Trial ID: NCT03833661*. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03833661 [Accessed 28 Aug 2020].

5 NICE. *Liver cancers overview.* 2020. Available from: https://pathways.nice.org.uk/pathways/liver-cancers#content=view-index&path=view%3A/pathways/liver-cancers/liver-cancers-overview.xml [Accessed 19 Aug 2020].

6 A Lamarca, D Palmer, H Wasan, P Ross, Y Ma, A Arora, et al. ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. *Journal of Clinical Oncology*. 2019 May;37(15 supplement):4003. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.4003.

7 Merck. *Bintrafusp alfa - TGFbeta trap/anti-PD-L1 for Biliary Tract Cancer.* 2020. Available from: https://www.merckgroup.com/en/research/healthcare-pipeline.html [Accessed 18 Aug 2020].

8 Clinicaltrials.gov. *Phase II and Phase III clinical trials for bintrafusp alfa.* 2020. Available from: https://clinicaltrials.gov/ct2/results?term=bintrafusp+alfa&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 19 Aug 2020].

9 Cancer Research UK. *What is bile duct cancer?* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/about [Accessed 07 Aug 2020].

10 Macmillan. *Bile duct cancer.* 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/bile-duct-cancer [Accessed 07 Aug 2020].
11 NHS. *Key facts - Bile duct cancer* 2020. Available from: https://www.nhs.uk/conditions/bile-duct-cancer/ [Accessed 07 Aug 2020].
12 The Alan Morement Memorial Fund (AMMF). *What is Cholangiocarcinoma?* 2015. Available from: https://ammf.org.uk/about-cholangiocarcinoma/ [Accessed 07 Aug 2020].
13 Macmillan. *Causes and risk factors of bile duct cancer.* 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/bile-duct-cancer/causes [Accessed 07 Aug 2020].
14 NHS. *Causes - Bile duct cancer.* 2020. Available from: https://www.nhs.uk/conditions/bile-duct-cancer/causes/ [Accessed 07 Aug 2020].
15 The Alan Morement Memorial Fund (AMMF). *Causes and risk factors of cholangiocarcinoma.* 2015. Available from: https://ammf.org.uk/causes-and-risk-factors/ [Accessed 07 Aug 2020].
16 Cancer Research UK. *Risks and causes - Bile duct cancer.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/risks-causes [Accessed 07 Aug 2020].
17 American Cancer Society. *Understanding advanced cancer, metastatic cancer, and bone metastasis* 2016. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html [Accessed 07 Aug 2020].
18 National Cancer Institute (NCI). *Cancer Staging.* 2015. Available from: https://www.cancer.gov/about-cancer/diagnosis-staging/staging [Accessed 18 Aug 2020].
19 Kim J, Hurria A. Determining Chemotherapy Tolerance in Older Patients With Cancer. *Journal of the National Comprehensive Cancer Network*. 2013 Dec;11(12):1494-502. Available from: https://doi.org/10.6004/jnccn.2013.0176.
20 Cancer Research UK. *Symptoms - Bile duct cancer.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/symptoms [Accessed 07 Aug 2020].
21 The Alan Morement Memorial Fund (AMMF). *Cholangiocarcinoma symptoms.* 2015. Available from: https://ammf.org.uk/symptoms/ [Accessed 07 Aug 2020].
22 NHS. *Symptoms - Bile duct cancer* 2020. Available from: https://www.nhs.uk/conditions/bile-duct-cancer/symptoms/ [Accessed 07 Aug 2020].
23 Genus T, Tataru D, Morement H, Toledano M, Khan S. Incidence and mortality rates of cholangiocarcinoma in England. *Annals of Oncology*. 2019 Jul;30(Supplement 4):IV155. Available from: https://www.annalsofoncology.org/article/S0923-7534(19)30962-7/fulltext.
24 The Alan Morement Memorial Fund (AMMF). *Cholangiocarcinoma mortality higher than incidence?* 2015. Available from: https://ammf.org.uk/2015/06/25/cholangiocarcinoma-mortality-higher-than-incidence/ [Accessed 28 Aug 2020].
25 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19.* 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 19 Aug 2020].
26 Cancer Research UK. *Survival - Bile duct cancer.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival [Accessed 18 Aug 2020].
27 The Alan Morement Memorial Fund (AMMF). *Treatment options for cholangiocarcinoma.* 2020. Available from: https://ammf.org.uk/treatment-options-2/ [Accessed 18 Aug 2020].
28 NHS. *Treament options - Bile duct cancer* 2020. Available from: https://www.nhs.uk/conditions/bile-duct-cancer/treatment/ [Accessed 18 Aug 2020].
29 NICE. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations.* 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10619/documents/final-scope [Accessed 19 Aug 2020].
30 Tella S, Kommalapati A, Borad M, Mahipal A. Second-line therapies in advanced biliary tract cancers. *The Lancet Oncology*. 2020 Jan;21(1):e29-e41. Available from: https://doi.org/10.1016/s1470-2045(19)30733-8.
31 Valle J, Borbath I, Khan S, Huguet F, Gruenberger T, Arnold D. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Gastrointestinal Cancers*. Sep 2016;27(Supplement 5):V28-37. Available from: https://www.esmo.org/guidelines/gastrointestinal-cancers/biliary-cancer.
32 National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers*. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf (login required). [Accessed 23 Sep 2020].

33 Bridgewater J, Galle P, Khan S, Llovet J, Park J, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of Hepatology*. 2014 Jun;60(6):1268-89. Available from: https://doi.org/10.1016/j.jhep.2014.01.021.

34 British Society of Gastroenterology. *Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update* Last Update Date: Aug 2012. Available from: https://doi.org/10.1136/gutjnl-2011-301748 [Accessed 18 Aug 2020].

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