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HEALTH TECHNOLOGY BRIEFING
OCTOBER 2021

Durvalumab in addition to gemcitabine and cisplatin for advanced biliary tract cancer – first line

NIHRIO ID	27415	**NICE ID**	10704
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	663171

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Durvalumab in combination with gemcitabine plus cisplatin is being developed for patients with advanced biliary tract cancer (BTC). 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 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 but the disease has a poor prognosis. There is a need for alternative treatments such as biological therapies.

Durvalumab is a drug designed to recognise and attach to a protein called 'programmed death-ligand 1' (PD-L1), which is present on the surface of many cancer cells. PD-L1 acts to switch off immune cells that would otherwise attack the cancer cells. By attaching to PD- L1 and blocking its effects, durvalumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease. Durvalumab is administered intravenously (IV). If licensed, durvalumab in addition to gemcitabine and cisplatin will offer an additional first line treatment option for advanced BTC.

PROPOSED INDICATION

First-line treatment for adults with advanced, unresectable or metastatic BTC.[1]

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi, MEDI4736) is an Fc optimised monoclonal antibody directed against PD-L1, with potential immune checkpoint inhibitory and antineoplastic activities. Upon intravenous administration, durvalumab binds to PD-L1, thereby blocking its binding to and activation of its receptor programmed death (PD-1) expressed on activated T cells. This may reverse T-cell inactivation and activate the immune system to exert a cytotoxic T-lymphocyte (CTL) response against PD-L1- expressing tumour cells. PD-L1, a member of the B7 protein superfamily, is overexpressed on certain tumour cell types and on various tumour-infiltrating immune cells. PD-L1 binding to PD-1 on T cells suppresses the immune system and results in increased immune evasion. The Fc region of durvalumab is modified in such a way that it does not induce either antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).[2,3]

In the phase III trial (NCT03875235), IV infusion every 3 weeks of durvalumab with gemcitabine plus cisplatin will be administered up to 8 cycles followed by monotherapy every 4 weeks until disease progression or other discontinuation criteria.[1]

INNOVATION AND/OR ADVANTAGES

Advanced, unresectable BTC represents an area of unmet medical need due to its aggressive nature, limited treatment options, and poor prognosis. BTCs express PD-L1 and high levels of soluble PD-L1 correlate with poor prognosis in BTC patients treated with chemotherapy. PD-1/PD-L1 antagonists such as durvalumab in combination with cytotoxic chemotherapy may contribute to a more effective antitumour immune response. Early clinical data demonstrate safety and efficacy for durvalumab as a single agent, but also in combination with chemotherapy in patients with BTC.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.[5]

Durvalumab is indicated in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).[5]

The most frequent adverse effects (≥10%) associated with durvalumab monotherapy include upper respiratory tract infections, hypothyroidism, cough/productive cough, diarrhoea, abdominal pain, rash, pruritus and pyrexia. The most frequent adverse effects associated with durvalumab given in combination with chemotherapy are neutropenia, anaemia, thrombocytopenia, leukopenia, decreased appetite, cough/productive cough, nausea, constipation, vomiting, alopecia and fatigue.[5]

Durvalumab is currently in 431 phase II/III studies for several oncology indications including:[6]

- hepatocellular carcinoma
- bladder cancer
- gastric cancer
- advanced solid tumours
- NSCLC
- pancreatic cancer
- cervical cancer

PATIENT GROUP

DISEASE BACKGROUND

Bile duct cancer, or cholangiocarcinoma, is the most common of the BTCs, and is a rare type of primary liver cancer that affects the biliary system. Bile ducts are small tubes that connect the liver and gallbladder to the small intestine, which produce bile to help break down fats in food.[7-10] The biliary system is made up of branch-like ducts that run throughout the liver called intrahepatic ducts (intrahepatic cholangiocarcinoma) and a duct that comes from the gallbladder called a cystic duct, which converge to form the common bile duct (extrahepatic cholangiocarcinoma). The common bile duct is located outside of the liver, behind the pancreas, and transports bile to the small intestine to aid digestion.[7,10] The other biliary tract cancers are gallbladder cancer and ampullary (or ampulla of Vater) cancer. Gallbladder cancer originates in the cells of the gallbladder. Most are adenocarcinomas, which begin in the gland cells of the gallbladder lining. Ampullary cancer is the rarest of the biliary tract cancers. This develops where bile ducts from the liver and pancreas join and enter the duodenum in an area known as the ampulla of Vater.[10]

The exact causes of BTC are not known, but certain factors can increase the risk of a person developing it. These include being over the age of 60, 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).[11-14]

Advanced cancer means that the cancer is not localised to one site and has metastasized (spread to other sites in the body). Patients with BTC that is locally advanced means the cancer has developed and remained in the biliary system, whereas metastatic BTC has spread from its primary location in the biliary system to other areas of the body. Treatment for advanced cancers aims to slow cancer spread, shrink the cancer area, relieve symptoms and increase life years.[15]

Average age of diagnosis is ≥ 65 years, with older patients at a higher risk of not being suitable for chemotherapy.[16] 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:[17-19]

- jaundice
- darker urine
- paler faeces
- itchy skin
- loss of appetite
- unintentional weight loss
- stomach pain and nausea
- 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, a type of BTC (ICD10 C22.1).[20] Due to the rarity and subtypes of alternative BTCs, it is difficult to estimate the number of individuals with 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).[21] Between 2020-21 in England the number of finished consultant episodes (FCE) for intrahepatic bile duct carcinoma (ICD-10 C22.1) was 8,914 with a total of 25,034 bed days.[22]

There are no UK-wide statistics for BTC survival by stage.[23] However, based on United States Surveillance, Epidemiology, and End Results Program (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.[23] For data in England (between 2001 and 2017) incidence and mortality rates of BTC are increasing, particularly for intrahepatic cholangiocarcinoma. The age-standardised incidence rate for cholangiocarcinoma in 2017 was 4.3 per 100,000, this rose from 2.7 per 100,000 (95% CI, 2.5-2.8) in 2001. If this increase continues, then by 2030 cholangiocarcinoma will no longer be a rare cancer.[20]

Public Health England data from 2008 and 2012 for all stages of BTC, showed that women diagnosed in England had a one-year survival rate of 25% (2012) and approximately a five-year survival rate of 5% (2008). Furthermore, 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).[23]

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.[8] 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. [24,25] Chemotherapy is also offered and may be used post-surgery to prevent relapse, to reduce cancer size or alongside radiotherapy in some cases.[8,25] 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.[25]

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.[24,26]

PLACE OF TECHNOLOGY

If licensed, durvalumab in addition to gemcitabine and cisplatin will offer an additional first line treatment option for advanced BTC.

CLINICAL TRIAL INFORMATION

Trial	**TOPAZ-1;** NCT03875235**;** A Phase III Randomized, Double-Blind Placebo Controlled, Multi-Regional, International Study of Durvalumab in Combination With Gemcitabine Plus Cisplatin Versus Placebo in Combination With Gemcitabine Plus Cisplatin for Patients With First-Line Advanced Biliary Tract Cancers **Phase III** - Recruiting **Location(s):** 4 EU countries, United Kingdom, United States and other countries. **Study completion date:** June 2022
Trial design	Randomised, parallel assignment, quadruple-masked.
Population	N = 757 (estimated), unresectable advanced or metastatic biliary tract, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma, previously untreated disease if unresectable or metastatic at initial diagnosis will be eligible; aged 18 years to 130 years.
Intervention(s)	Durvalumab IV infusion every 3 weeks with gemcitabine plus cisplatin
Comparator(s)	Placebo IV infusion every 3 weeks with gemcitabine plus cisplatin
Outcome(s)	Primary outcome; - Overall survival [Time Frame: 40 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Durvalumab is already indicated in the UK for the treatment of NSCLC and extensive-stage SCLC; a 120mg/2.4ml vial costs £592 and 500mg/10ml vial costs £2,466.[27]

RELEVANT GUIDANCE

NICE GUIDANCE

- 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.[28]
- European Society for Medical Oncology. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2016[29]
- US Mayo Clinic. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. January 2014[30]
- British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. August 2012[31]

ADDITIONAL INFORMATION

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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.