National Institute for Health Research

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Cabozantinib for Hepatocellular Carcinoma

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LAY SUMMARY

Liver cancer is the 17th most common cancer in the UK, accounting for 2% of all new cancer cases. Most common symptoms include significant weight loss, a swollen abdomen, yellowing of the skin and whites of the eyes, abdominal discomfort or pain, pain in the right shoulder, loss of appetite over weeks, being sick, feeling full or bloated after eating, itching, high temperatures and others. Cirrhosis, alcohol, non-alcoholic fatty liver disease, hepatitis viruses and diabetes are all considered risk factors.

Hepatocellular carcinoma (HCC) accounts for about 75% of all liver cancers. It is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis. HCC is most common in Asia and Africa, which is due to the high prevalence of hepatitis B and C. In the UK, there were 5,550 new cases of liver cancer in 2014.

Cabozantinib is a new biological treatment called a tyrosine kinase inhibitor or TKI. It stops signals that cancer cells use to divide and grow. It is currently being considered as a treatment option for patients who fail primary treatment with sorafenib.

TARGET GROUP

- For the treatment of advanced hepatocellular carcinoma in patients that fail sorafenib

TECHNOLOGY

DESCRIPTION

Cabozantinib [BMS 907351; BMS 907351 (capsule); BMS 907351 (liquid suspension); BMS 907351 (tablet); BMS-907351; BMS-907351 (capsule); BMS-907351 (liquid suspension); BMS-907351 (tablet); Cabometyx; Cabometyx (tablet); cabozantinib; cabozantinib (capsule); cabozantinib (liquid suspension); cabozantinib (tablet); cabozantinib-s-malate; cabozantinib-s-malate (capsule); cabozantinib-s-malate (liquid suspension); cabozantinib-s-malate (tablet); Cometriq; Cometriq (capsule); Cometriq (liquid suspension); Cometriq (tablet); XL 184; XL 184 (capsule); XL 184 (liquid suspension); XL 184 (tablet); XL-184; XL-184 (capsule); XL-184 (liquid suspension); XL-184 (tablet); XL184; XL184 (capsule); XL184 (liquid suspension); XL184 (tablet)] is a spectrum-selective kinase inhibitor (SSKI), developed by Exelixis and Bristol-Myers Squibb (BMS) for the treatment of cancer. It inhibits Met, Ret and VEGFR2.

Cabozantinib is licensed in the EU for patients

- with advanced renal cell carcinoma in adults following prior vascular endothelial growth factor targeted therapy
- with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma
- an orphan drug for the treatment of metastatic thyroid cancer

Outside of the EU cabozantinib is licensed to treat both thyroid cancer and renal cancer.

It is currently in phase III clinical trials for liver cancer, phase II clinical trials for myeloma and phase I clinical trial for prostate, urethral and bladder cancer.

In Phase III clinical trials cabozantinib is given orally at a does of one 60mg tablet a day.

INNOVATION and/or ADVANTAGES

If licensed, cabozantinib could offer a novel additional treatment option for patients with advanced hepatocellular carcinoma that fail sorafenib.

DEVELOPER

Exelixis

AVAILABILITY, LAUNCH or MARKETING

Cabozantinib is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Liver cancer is the 17th most common cancer in the UK, accounting for 2% of all new cases.[1] Most common symptoms include significant weight loss, a swollen abdomen, yellowing of the skin and whites of the eyes, abdominal discomfort or pain, pain in the right shoulder, loss of appetite over weeks, being sick, feeling full or bloated after eating, itching, high temperature and sweating.[2] What causes liver cancer is yet quite unknown, however, there are several risk factors, such as cirrhosis, alcohol, non-alcoholic fatty liver disease, Hepatitis viruses, smoking, low immunity, family history and diabetes.[3]

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis.[1] It is the most common primary liver cancer [4] and accounts for about 75% of all liver cancers.[5] The cells of origin are believed to be hepatic stem cells, although this remains the subject of investigation. Tumours progress with local expansion, intrahepatic spread, and distant metastases.[1]

HCC is an end result of some chronic infections with the Hepatitis B (HBV) or the Hepatitis C (HCV).[4] HCC is most common in Asia and Africa, which is due to the high prevalence of hepatitis B and hepatitis C. HCC is now the third leading cause of cancer deaths worldwide[1] and the sixth most common cancer-related death.[6] In Europe, prevalence of HCV infections is reported to be the main leading cause of HCC. Besides HCV and HBV, any agent leading to chronic injury and eventually cirrhosis constitutes an oncogenic agent. Aflatoxin, alcoholism, and non-alcoholic steatohepatitis (NASH) are important and prevalent in certain areas of the world. It is generally believed that the majority of HCCs develop in a progressively from acute hepatitis through various stages of chronic hepatitis, to cirrhosis, to HCC.[4]

CLINICAL NEED and BURDEN OF DISEASE

In 2014, there were 5,550 new cases of liver cancer in the UK: 3,652 (66%) in males and 1,898 (34%) in females, giving a male:female ration of around 18:10. The crude incidence rate shows that there are 12 new liver cancer cases for every 100,000 males in the UK, and 6 for every 100,000 females.[7]

The risk of developing HCC increases with age.[8] The overall incidence of HCC has more than doubled within the past 20 years – from 2.6 to 5.2 per 100,000 population. The numbers are twice as high in developing nations over developed countries.[1] The incidence varies from 3 out of 100,000 in Western countries, to more than 15 out of 100,000 in certain areas of the world.[6] HCC usually occurs 20 to 30 years after the initial liver insult.[9] Approximately 70% of cases occur in people over the age of 65 years.[8]

In 2014, 1,728 deaths were attributed to liver cell carcinoma in England and Wales.[10] In 2013-14, there were 3,911 admissions for liver cell carcinoma (ICD-10 C22.0) in England, resulting in 23,937 bed-days and 5,743 finished consultant episodes.[11]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. Hepatocellular carcinoma (advanced or metastatic) – sorafenib (first line) (review of TA189) [ID1012] – CDF rapid reconsideration process. Expected TBC.
- NICE Technology appraisal guidance in development. Lenvatinib for untreated advanced unresectable hepatocellular carcinoma [ID1089]. Expected May 2018.
- NICE Technology appraisal guidance in development. Regofarenib for previously treated unresectable hepatocellular carcinoma [ID991]. Expected December 2017.
- NICE Technology appraisal guidance. Sorafenib for the treatment of advanced hepatocellular carcinoma [TA189]. May 2010.
- NICE Clinical Guideline. Hepatitis B (chronic): diagnosis and management [CG165]. June 2013.
- NICE Interventional Procedure Guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer [IPG488].May 2014.
- NICE Interventional Procedure Guidance. Selective internal radiation therapy for primary hepatocellular carcinoma [IPG460]. July 2013.
- NICE Interventional Procedure Guidance. Irreversible electroporation for treating primary liver cancer [IPG444]. February 2013.
- NICE Interventional Procedure Guidance. Ex-vivo hepatic resection and reimplantation for liver cancer [IPG298]. April 2009.
- NICE Interventional Procedure Guidance. Microwave ablation of hepatocellular carcinoma [IPG214]. March 2007.
- NICE Interventional Procedure Guidance. Radiofrequency-assisted liver resection [IPG211].February 2007.
- NICE Interventional Procedure Guidance. Laparoscopic liver resection [IPG135]. July 2005.
- NICE Interventional Procedure Guidance. Radiofrequency ablation of hepatocellular carcinoma [IPG2]. July 2003.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2016 Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma. 16022/P
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a
- NHS England. 2013/14 NHS Standard Contract for Cancer: Pancreatic (Adult) – Section B Part 1 – Service Specifications. A02/S/b
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All ages). B01/S/a

OTHER GUIDANCE

No guidance is currently available.

CURRENT TREATMENT OPTIONS

Due to chronic viral B and C being the most common risk factors of carcinogenesis, prevention of HCC requires an effective risk control of infection. Therefore vaccination against Hepatitis B virus appears the best way for prevention. In western countries universal vaccination programmes should lead to significant decrease in HCC incidence.[4]

HCC treatment depends highly on tumour characteristics, liver function, and presence or not of metastasis or vascular invasion. Staging system of cancers for classification of HCC provides a guide to

patient assessment and to direct therapeutic interventions. Mostly used for HCC staging are such as Okuda classification, TNM classification, CLIP classification, BCLC classification, French classification, CUPI classification, and JIS classification. Curative treatments are surgical resection, liver transplantation, and percutaneous ablation and aim to improve survival. Palliative approaches include systemic chemotherapy, immunotherapy, and hormonal compounds. Curative options can be considered in early stages of HCC, which applies to only ⅓ of patients.[4]

Cabozantinib could be a useful agent for inhibiting tumour growth, angiogenesism and metastasis in HCC with dysregulated MET and VEGFR2 signalling pathways.[12]

EFFICACY and SAFETY

Trial	EudraCT Number: 2013-001001-91, NCT01908426, UKCRN ID 16858
Sponsor	Exelixis
Status	Open.
Source of Information	Trialtrove
Location	EU (incl. UK), USA and Canada and other countries.
Design	Randomised, efficacy, safety, placebo control, pharmacokinetics, double blind/blinded, multiple arm
Participants	N=760. > or = 18 years old on the day of consent ECOG performance status of 0 or 1. Patients with advanced hepatocellular cancer (HCC) and prior sorafenib exposure. Histological or cytological diagnosis of HCC. The subject has disease that is not amenable to a curative treatment approach (eg. Transplant, surgery, radiofrequency ablation). Progression following at least 1 prior systemic treatment for HCC. Recovery to = Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy.
Schedule	Patients will be randomized 2:1. Experimental: Cabozantinib (XL 184) Assigned Interventions Cabozantinib (XL184): oral cabozantinib tablet once a day Other Name: XL184 Arms: Placebo Comparator: Placebo Assigned Interventions Oral cabozantinib-matched placebo tablet once daily Drug: placebo ASCO 2014: Subjects are randomized 2:1 to receive either cabozantinib 60mg daily or placebo. Stratification factors are etiology of disease, geographic region and the presence of extrahepatic spread of disease and/or macrovascular invasion.
Follow-up	Not reported.
Primary Outcomes	Effect of Cabozantinib (XL184) compared with placebo on overall survival in subjects with advanced hepatocellular carcinoma who have received prior sorafenib. Efficacy and safety of cabozantinib compared with placebo.
Secondary Outcomes	Overall survival.
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Not reported.

TIMATED COST and IMPACT

COST

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

- ☒ Reduced mortality/increased length of survival
- ☒ Reduced symptoms or disability
- ☒ Other: improved patient convenience
- ☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- ☐ Increased use of existing services
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other
- ☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- ☐ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs
- ☐ Other reduction in costs
- ☐ Other
- ☒ None identified

OTHER ISSUES

- ☐ Clinical uncertainty or other research question identified
- ☒ None identified

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