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Ramucirumab for advanced hepatocellular carcinoma – second line

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LAY SUMMARY

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and occurs mainly in patients with underlying chronic liver disease and cirrhosis. Advanced (metastatic) HCC occurs when the cancer has spread to lymph nodes or to other organs. HCC can produce markers that can be detected by a blood test. One of the markers produced by HCC is called alpha fetoprotein (AFP). AFP level can reflect the tumour responsiveness to treatment. The cancer medicine, sorafenib is the recommended first line treatment option for HCC. However, some patients may not respond to this medicine or they may be intolerant to it and may require other treatments (second line).

Ramucirumab is being investigated in clinical trials as a second line treatment for patients with advanced HCC who have elevated baseline AFP, and also in patients who are either intolerant to sorafenib therapy or whose HCC progressed following treatment with sorafenib therapy. Ramucirumab is given as intravenous (IV) injection and acts by preventing tumour growth by slowing the formation of new blood vessels which supply the tumour cells with blood. It is already approved for the treatment of certain types of advanced cancers such as stomach cancer, colorectal cancer and non-small cell lung cancer. If licensed, ramucirumab may offer a new second line treatment option for patients with advanced HCC who have elevated baseline AFP and have not responded or are intolerant to the first line treatment

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TARGET GROUP

Hepatocellular carcinoma (advanced, baseline alpha-fetoprotein (AFP) ≥ 400ng/ml, progressed after treatment with, or intolerant to sorafenib therapy) – second line.

TECHNOLOGY

DESCRIPTION

Ramucirumab (Cyramza; IMC-1121B) is a vascular endothelial growth factor (VEGF) receptor 2 antagonist. VEGF receptor 2 is involved in angiogenesis –the formation of new blood vessels from pre-existing ones. Some cancerous tumours create VEGF proteins, which attach to VEGF receptors of existing blood vessel cells causing new blood vessels to form around the tumours, giving a tumour its own blood supply and allowing it to grow and spread. Ramucirumab binds to VEGF receptor 2 and blocks the binding of the VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. In an in vivo animal model, ramucirumab inhibited angiogenesis. Blocking the VEGF protein from linking to the blood vessels helps to inhibit tumour growth by slowing angiogenesis and the blood supply that feeds tumours.[1]

Ramucirumab is available as a concentrate to be made up into a solution for intravenous infusion (drip).[2] In the phase III clinical trial, REACH-2 (NCT02435433), ramucirumab is given as 8 milligrams per kilogram (mg/kg) administered as an intravenous (IV) injection on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.[3]

Ramucirumab is a cancer medicine that is approved by the European Medicines Agency (EMA) to treat adult patients with advanced gastric cancer or gastro-oesophageal adenocarcinoma, metastatic colorectal cancer and in non-small cell lung cancer that is advanced or has spread to other parts of the body.2

The most serious adverse reactions associated with ramucirumab treatment (as a single agent or in combination with cytotoxic chemotherapy) are gastrointestinal perforation, severe gastrointestinal haemorrhage, and arterial thromboembolic events. The most common adverse reactions observed in ramucirumab-treated patients are neutropenia, leukopenia, thrombocytopenia, hypoalbuminaemia, hypertension, epistaxis, gastrointestinal haemorrhage events, stomatitis diarrhoea, proteinuria, fatigue/asthenia, and peripheral oedema.[4]

Ramucirumab is in phase III stage of development for the following indications:[5]

- Non-small cell lung cancer (first line therapy)
- Adenocarcinoma of the gastroesophageal junction (first line therapy)
- Gastric cancer (first line therapy)
- Bladder cancer (second line therapy)
- Metastatic transitional (urothelial) tract cancer (second line therapy)

Ramucirumab is in phase II stage of development for the following indications:[5]

- Gallbladder cancer (first line therapy, second line therapy)
- Fallopian tube cancer
- Neuroendocrine tumours
- Epithelial ovarian cancer
- Gastric cancer (second line therapy)
- Metastatic biliary tract cancer (first line therapy, second line therapy)
- Metastatic breast cancer (second line therapy)

- Gastroesophageal (GE) junction carcinomas (second line therapy)
- Metastatic renal cell carcinoma (second line therapy)
- Peritoneal tumour
- Signet ring cell squamous cell carcinoma (second line therapy)

INNOVATION and/or ADVANTAGES

The absence of a licenced second-line therapy for patients with advanced hepatocellular carcinoma who have failed the first line, sorafenib, represents an urgent unmet medical need.[6] Outcomes of the phase III REACH trial; NCT01140347 showed that a clinically meaningful improvement in overall survival (OS) was observed in populations with a baseline AFP ≥400 ng/mL or ≥1.5 × ULN.[7,8] This prompted a second study, the REACH-2 trial (Phase III study of ramucirumab and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma and elevated baseline AFP following first-line therapy with sorafenib) which is currently running.[3, 8] If licensed, ramucirumab may offer a new treatment option (as a second line) for patients with advanced hepatocellular carcinoma who have baseline AFP ≥ 400ng/ml, and have progressed after treatment with, or are intolerant to sorafenib therapy.

DEVELOPER

Eli Lilly & Co Ltd

REGULATORY INFORMATION/ MARKETING PLANS

Ramucirumab is a designated orphan drug in the USA for the treatment of hepatocellular carcinoma in 2011.[9]

PATIENT GROUP

BACKGROUND

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Cancers are named after their original cell type, from the organ where the cancer first begins to grow. HCC is a primary cancer of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis. This is important because cancers are treated according to the original cell type.[10, 11]

Liver cancer is classified by stage of progression, from stage I through IV. As a rule, the lower the number, the less the cancer has spread. A higher number, such as stage IV, means cancer has spread to a greater extent. Advanced (metastatic) cancer mean that the tumour has spread to lymph nodes or other organs.[12]

HCC can produce a marker that can be picked up on a blood test. A marker is a chemical that is made by particular types of cancer cells and found in the blood at higher than normal levels. One of the markers in HCC is called alpha fetoprotein (AFP). Not all HCCs produce this marker, and people who have liver cirrhosis can also have raised levels of this marker and not have HCC. So, this blood test alone would not be reliable enough to use for the whole population.[13]

Signs and symptoms of liver cancer often do not show up until the later stages of the disease. Most patients (80%) with HCC will be diagnosed with advanced stage disease. Signs and symptoms of liver cancer include an enlarged, irregular, and nodular liver, weight loss, swelling or fluid build-up in the abdomen, jaundice, loss of appetite over a period of a few weeks, nausea or vomiting, feeling full or bloated after eating (even after a small meal), itching, a sudden worsening of health in somebody with

known chronic hepatitis or cirrhosis, a high temperature and sweating, an enlarged spleen, and pain in the abdomen or near the right shoulder blade.[14, 15,16]

Risk factors for liver cancer include cirrhosis, excessive alcohol intake, non-alcoholic fatty liver disease, long term infection with hepatitis B or C, smoking, low immunity, systemic lupus erythematous, family history of liver cancer, diabetes, gallbladder removal, radiation from x-rays or scans, being overweight or obese, and exposure to some substances, including some chemicals.[17]

HCC is the third most common cause of cancer-related death. The majority of patients receive palliation because of late-stage presentation, multiple comorbidities, associated hepatic dysfunction, and limited donor liver availability. The vast majority of patients with advanced cancer report that quality of life (QoL) is at least as important as length of survival. Sometimes, palliative treatments may negatively influence QoL especially if complication ensue which may have a negative impact on the willingness of the patients to continue and comply with future treatment. [18]

CLINICAL NEED and BURDEN OF DISEASE

In 2015, there were 5,736 new cases of liver cancer in the UK: 3,685 (64%) in males and 1,898 (36%) in females. The crude incidence rate shows that there are 11.5 new liver cancer cases for every 100,000 males in the UK, and 6.2 for every 100,000 females.[19]

Most liver cell carcinomas are HCCs. The data from 2010-2012 in the UK shows that most liver cancer cases in males were liver cell carcinomas, whereas in females liver cell carcinomas were the second most common type of liver cancer after intrahepatic bile duct carcinomas. The percentage of liver cell carcinomas was 61.1% and 31.8% in males and females respectively.[19]

NHS Digital, Hospital Episode Statistics for England 2016-17 shows that there were 4,856 hospital admissions for liver cell carcinoma (ICD 10 code: C22.0), 7,474 Finished Consultant Episodes (FCE), and 24,178 FCE bed days.[20]

For HCC, men experienced a rise in the mortality rate (from 1.49 to 2.60 per 100,000 in 1996 to 2008 respectively) whereas women had a relatively stable rate.[21]

Around a quarter of people in England diagnosed with liver cancer aged 15-39 survive their disease for five years or more, compared with around 5 in 100 people diagnosed aged 80 and over (2009-2013).[22]

The population likely to be eligible to receive ramucirumab could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for previously treated advanced hepatocellular carcinoma (ID1141). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for untreated advanced hepatocellular carcinoma (1248). Expected date of issue to be confirmed.
- NICE technology appraisal in development. ADI-PEG 20 for previously treated hepatocellular carcinoma (ID1025). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Doxorubicin nanoparticles for previously treated advanced hepatocellular carcinoma (ID1314). Expected date of issue to be confirmed.

- NICE technology appraisal in development. Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma (ID1089). Expected October 2018.
- NICE technology appraisal in development. Regorafenib for previously treated unresectable hepatocellular carcinoma (ID991). Expected March 2018.
- NICE technology appraisal. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.
- 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 (IPG002). July 2003.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- The American Association for the Study of Liver Diseases. AASLD guidelines for the treatment of hepatocellular carcinoma. 2018.[23]
- Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. 2017.[24]
- Barts Health NHS Trust, Royal Free London NHS Trust, and London Cancer North and East. Hepatic pancreatic and biliary (HPB) faculty clinical guideline: management of patients with hepatocellular carcinoma (HCC). 2014.[25]
- The European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC). Management of hepatocellular carcinoma, EASL-EORTC clinical practice guidelines. 2012.[26]
- European Society for Medical Oncology (ESMO) and European Society of Digestive Oncology (ESDO). Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012.[27]
- British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. 2003.[28]

CURRENT TREATMENT OPTIONS

When surgery is not possible to remove the cancer, the patient may have local treatments to the liver. These include chemoembolization, radiofrequency ablation, alcohol (ethanol) injections into the

tumour, radioembolisation and microwave ablation. Patients with unresectable and advanced cancer may also have biological therapy, chemotherapy or radiotherapy.[29] There are no available treatments as second-line therapy for patients who have failed or are intolerant to sorafenib.[26, 6] ESMO–ESDO guidelines recommend that in case of progression or intolerance to sorafenib, best supportive care is preferred or patients should be included in clinical trials.[27] Best supportive care may involve palliative and supportive care for disease-related symptoms and toxicity associated with treatment as deemed medically necessary and appropriate.[30]

EFFICACY and SAFETY

Trial	**REACH-2, NCT02435433; ramucirumab vs placebo; phase III**
Sponsor	Eli Lilly and Company.
Status	Ongoing, recruiting.
Source of Information	Trial registry.[3]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, double-blind.
Participants	n=383 (planned); aged 18 years and older; advanced HCC with baseline AFP ≥400 nanograms/millilitre; progressed after treatment with, or intolerant to sorafenib therapy.
Schedule	Randomised to: - Ramucirumab: 8 milligrams per kilogram (mg/kg) ramucirumab administered as an intravenous (IV) injection on day 1 of each 14 day cycle; - Placebo: administered IV on day 1 of each 14 day cycle; - Open Label Ramucirumab: 8 mg/kg ramucirumab administered IV on day 1 of each 14 day cycle; - Ramucirumab ME2 Cohort: 8 mg/kg ramucirumab administered IV on day 1 of each 14 day cycle; - Placebo (ME2 cohort): administered IV on day 1 of each 14 day cycle.
Follow-up	Active treatment period: participants may continue treatment until discontinuation criteria are met. Follow-up approximately 28 months.
Primary Outcomes	Overall Survival (OS) [time frame: baseline to death from any cause (approximately 28 months)]
Secondary Outcomes	• Progression free survival [time frame: baseline to objective progression or death from any cause (approximately 28 months)] • Time to radiographic progression [time frame: baseline to objective progression (approximately 28 months)] • Percentage of participants with a best overall response of complete response or partial response: objective response rate [time frame: baseline to objective progression (approximately 28 months)] • Pharmacokinetics: serum concentration of ramucirumab [time frame: predose cycle 1 through follow up (approximately 28 Months)]

	• Number of participants with anti-ramucirumab antibodies [Time frame: predose cycle 1 through follow up (approximately 28 months)] • Functional assessment of cancer therapy hepatobiliary symptom index-8 [time frame: baseline through end of study (approximately 28 months)] • EuroQol 5-Dimension 5-Level questionnaire [time frame: baseline through end of study (approximately 28 months)] • Time to deterioration in eastern cooperative oncology group performance status [time frame: baseline through end of study (approximately 28 months)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as June 2020.

Trial	**REACH, NCT01140347; ramucirumab vs placebo, both in combination with best supportive care (BSC); phase III**
Sponsor	Eli Lilly and Company.
Status	Complete, published.
Source of Information	Trial registry,[30] publication,[31] abstract,[7] manufacturer.[32]
Location	EU (not including UK), USA, Canada and other countries.
Design	Multicentre, randomised, placebo-controlled (placebo plus BSC), double-blind
Participants	n=565; aged 18 Years and older; males and females; advanced HCC; previously treated with sorafenib.
Schedule	Randomised to ramucirumab 8 milligrams/kilogram (mg/kg) intravenous (IV) every 2 weeks; or Placebo 8 mg/kg IV every 2 weeks; both in combination with BSC
Follow-up	Active treatment duration: every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. The median duration of therapy was 12·0 weeks (The interquartile range (IQR) 6·0–29·4) for the ramucirumab group versus 8·0 weeks (6·0–17·8) for the placebo group. Median follow-up for the ramucirumab group was 8·3 months (IQR 4·0–14·9) and for the placebo group was 7·0 months (3·2–12·9).
Primary Outcomes	• Overall survival [time frame: randomization to death from any cause (up to 37 months)]
Secondary Outcomes	• Time Frame: Randomization until date of objectively determined progressive disease (PD) (up to 36 months): 1. PFS 2. TTP

	• Percentage of participants with a best overall response of CR or PR [ORR] time frame: baseline to the date of first evidence of confirmed CR or PR (up to 37 months) • Number of participants with adverse events (AEs) and the number of participants who died [time frame: baseline to study completion (up to 37 months)] • Time Frame: 1 hour following the completion of cycle 1 (14-day cycle) infusion 1. Maximum Concentration (Cmax) of Ramucirumab, Cycle 1 2. Cmax of Ramucirumab, Cycle 4 3. Cmax of Ramucirumab, Cycle 7 • Number of participants with treatment emergent positive anti-ramucirumab response [serum anti-ramucirumab antibody assessment (immunogenicity)] [time frame: prior to treatment and 1 hour post end of infusion for cycles 1, 4 and 7 (14-day cycles)]
Key Results	Between Nov 4, 2010, and April 18, 2013, 565 patients were enrolled, of whom 283 were assigned to ramucirumab and 282 were assigned to placebo. Median overall survival for the ramucirumab group was 9·2 months (95% CI 8·0–10·6) versus 7·6 months (6·0–9·3) for the placebo group (HR 0·87 [95% CI 0·72–1·05]; p=0·14). Grade 3 or greater adverse events occurring in 5% or more of patients in either treatment group were ascites (13 [5%] of 277 patients treated with ramucirumab *vs* 11 [4%] of 276 patients treated with placebo), hypertension (34 [12%] *vs* ten [4%]), asthenia (14 [5%] *vs* five [2%]), malignant neoplasm progression (18 [6%] *vs* 11 [4%]), increased aspartate aminotransferase concentration (15 [5%] *vs* 23 [8%]), thrombocytopenia (13 [5%] *vs* one [<1%]), hyperbilirubinaemia (three [1%] *vs* 13 [5%]), and increased blood bilirubin (five [2%] *vs* 14 [5%]).[31] Interpretation: second-line treatment with ramucirumab did not significantly improve survival over placebo in patients with advanced HCC. No new safety signals were noted in eligible patients and the safety profile is manageable.[31] Phase III REACH trial did not meet its primary endpoint; overall survival favoured the ramucirumab arm but was not statistically significant.[32] Pre-specified subgroup analysis was performed based on baseline AFP with a cut-off of 400 ng/mL. In 250 patients with baseline AFP ≥400 ng/mL (ramucirumab arm (RAM)) 119; Placebo arm (PBO) 131), OS HR was 0.67 (95% CI 0.51–0.90; p=0.0059). Median OS was 7.8m for RAM vs 4.2m for PBO. In 417 patients with a baseline AFP ≥1.5 × upper limit of normal (ULN; RAM 205; PBO 212), mOS was 8.6m for RAM vs 5.7m for PBO and the HR was 0.749 (95% CI: 0.603, 0.930) (p=0.0088). The interaction testing of baseline AFP and RAM treatment effect on OS using both cut-offs (400 ng/mL and 1.5 x ULN) are significant (p-value = 0.0272 and 0.0372, respectively).[7] Conclusions: A clinically meaningful improvement in OS was observed in populations with a baseline AFP ≥400 ng/mL or ≥1.5 × ULN. Additional analyses demonstrated a consistent RAM OS benefit for the patient population with baseline AFP over a wide range of values above the normal range. Baseline AFP is a likely predictive marker for RAM OS benefit.[7]

Adverse effects (AEs)	The most frequently reported (≥1%) treatment-emergent serious adverse event of any grade or grade 3 or more was malignant neoplasm progression. The safety profile in the subgroup analysis (patients with baseline AFP ≥400 ng/mL) was similar to that observed in the overall safety population.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Ramucirumab is already marketed in the UK. The NHS indicative price for Cyramza vials (Eli Lilly and Company Ltd):[33]

- 100mg/10ml concentrate for solution for infusion (1 vial) costs £500
- 500mg/50ml concentrate for solution for infusion (1 vial) costs £2,500

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services: patient visits for infusion every 2 weeks including accompanying labs and CT scans

☐ 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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