Lenvatinib (Lenvima) for unresectable hepatocellular carcinoma – first line

LAY SUMMARY

Hepatocellular carcinoma is the most common type of liver cancer. Most cases of hepatocellular carcinoma are caused by cirrhosis, where the liver is damaged and scarred because of excessive alcohol intake, long term infection with hepatitis B or C, or fatty liver disease. It is more common in men than women and typically affects older people.

Lenvatinib is a new type of drug that is taken as a capsule by mouth. Some studies have suggested that lenvatinib may help patients with hepatocellular carcinoma when other treatments are no longer working. Another study is trying to show how well it works and that it is safe to use. If licensed for use in the UK, lenvatinib could be a new first line treatment option for people with hepatocellular carcinoma.

NIHR HSRIC ID: 8621
TARGET GROUP

- Hepatocellular carcinoma: advanced unresectable or metastatic – first line.

TECHNOLOGY

DESCRIPTION

Lenvatinib (Lenvima; E-7080; ER-203492-00; lenvatinib mesylate) is a multi-targeted tyrosine kinase inhibitor. This drug selectively inhibits the kinase activities of all vascular endothelial growth factor receptors, in addition to other proangiogenic and oncogenic pathways, including fibroblast growth factor receptors, the platelet derived growth factor receptor alpha, KIT\textsuperscript{a} and RET\textsuperscript{b}. In the phase III clinical trial, lenvatinib is administered orally once daily at a dose of either 8mg or 12mg; treatment continues until disease progression or unacceptable toxicity\textsuperscript{1}.

Lenvatinib is licensed in the EU for the treatment of adult patients with progressive or locally advanced or metastatic differentiated thyroid carcinoma, refractory to radioactive iodine\textsuperscript{2}. The most frequently reported adverse reactions are hypertension, diarrhoea, decreased appetite, decreased weight, fatigue, nausea, proteinuria, stomatitis, vomiting, dysphonia, headache, and palmar-plantar erythrodysesthesia syndrome\textsuperscript{5}. Hypertension and proteinuria tend to occur early during lenvatinib treatment\textsuperscript{2}.

Lenvatinib is in preregistration phase for late-stage renal cancer. It is also in phase II clinical trials for late-stage endometrial cancer, late-stage malignant melanoma and late-stage non-small cell lung cancer.

INNOVATION and/or ADVANTAGES

If licensed, lenvatinib will offer an additional oral first line treatment option for unresectable hepatocellular carcinoma.

DEVELOPER

Eisai Co. Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Hepatocellular cancer (HCC) is a malignant tumour arising from liver cells (hepatocytes)\textsuperscript{3}. It is sometimes known as hepatoma and is usually confined to the liver, although occasionally it spreads to other organs\textsuperscript{4}. The liver plays an important role in the storage of nutrients, the

\textsuperscript{a} v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog.
\textsuperscript{b} Rearranged during transfection proto-oncogene.
production of bile and protein, and the breakdown of harmful and waste products\(^5\). HCC affects more men than women and the incidence increases with age\(^4\). HCC commonly occurs on a background of chronic liver disease, mainly alcoholic or viral (hepatitis B or C), and presents in patients with cirrhosis in about 90% of cases. Other risk factors include insulin resistance associated with non-alcoholic steatohepatitis, diabetes, and obesity\(^5\), as well as smoking, infections and alcohol consumption\(^4\).

### NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

### CLINICAL NEED and BURDEN OF DISEASE

Liver cancer is the 18\(^{th}\) most commonly diagnosed cancer in the UK, accounting for 1% of all new cases of cancer, a figure that is continuing to rise\(^7\). In 2013, there were 4,387 new cases of liver cancer in England, 2,799 (64%) in males and 1,588 (36%) in females\(^8\). HCC is the most common type of primary liver cancer, accounting for about 85% of cases\(^9\). The incidence of HCC has increased in recent years as a result of the rising prevalence of infection with hepatitis C virus and increased alcohol consumption\(^10,11\). Approximately 40-50% of HCCs in Europe can be attributed to excessive alcohol consumption\(^12\). The estimated number of HCC patients with advanced stage disease and for whom surgical or locoregional therapies have failed or are not suitable is 25-35%\(^5\), though expert opinion notes that many patients in this group have advanced liver disease or poor performance status, and tolerate any treatment poorly\(^c\).

In 2014-15 there were 11,079 admissions for HCC (ICD-10 C22.0) in England, resulting in 61,822 bed days and 15,676 finished consultant episodes\(^13\). During 2014, there were 4,452 registered deaths from HCC in England and Wales\(^14\).

### PATIENT PATHWAY

### RELEVANT GUIDANCE

**NICE Guidance**

- NICE interventional procedure guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer (IPG488). May 2014.

\(^c\) Expert personal opinion.
Horizon Scanning Research & Intelligence Centre


Other Guidance

- European Society for Medical Oncology. Hepatocellular Carcinoma: ESMO-ESDO Clinical Practice Guidelines. 2012\textsuperscript{15}.

CURRENT TREATMENT OPTIONS

For the majority of patients with HCC, treatment is palliative rather than curative. The only potentially curative options for HCC are surgery (including transplantation) or ablation in selected patients\textsuperscript{d}. Treatment options include\textsuperscript{d,5,14,15,16,17,18,19,20}:

- Sorafenib – considered the standard of care for advanced HCC with well-preserved liver function by some authorities, but is not recommended by NICE.
- Chemoembolisation – transarterial chemoembolisation (TACE) with doxorubicin or cisplatin. TACE is the most widely used primary treatment for HCC not amenable to curative treatment by excision or ablation. TACE is recommended for patients with BCLC\textsuperscript{e} stage B (intermediate), or those with good liver function (patients with Childs Pugh A and B7/8 disease) and multinodular asymptomatic tumours without macroscopic vascular invasion or extra hepatic spread; however, it cannot be used as a single modality treatment to cure intermediate HCC. Studies with doxorubicin-loaded DC clotting beads (DEBDOX) suggest there is less leakage of chemotherapy into the systemic circulation than conventional TACE, resulting in fewer side effects, with at least the same activity.
- Hepatic resection – surgery is the most effective treatment for primary liver cancer and the standard treatment for HCC, but requires well preserved liver function.
- Liver transplantation – to be eligible patients must have a single tumour ≤5cm, or a single tumour between 5-7cm stable for at least 6 months, or up to 5 tumours that are <3cm.
- Radiofrequency ablation – more effective for treating small HCCs (≤3cm in diameter). In tumours less than 3cm it has also demonstrated clinical effectiveness equal to surgical resection.

\textsuperscript{d} Expert personal communication.
\textsuperscript{e} Barcelona Clinic Liver Cancer (BCLC) staging system.
EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01761266; E7080-G000-304; lenvatinib vs sorafenib; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Eisai Limited.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Poster¹, trial registry²¹, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=954 (planned); aged 18 years and older; unresectable HCC; no prior anticancer agents; at least one measurable target lesion (measured by mRECIST³ criteria); stage B or C on BCLC; Child-Pugh score A; ECOG⁴ performance score 0 or 1.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to lenvatinib at 8mg (if body weight &lt;60kg) or 12mg (if body weight ≥60kg) orally once daily; or sorafenib at 400mg orally twice daily; both as a 28 day cycle.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment until disease progression, unacceptable toxicity or death. Follow-up until date of death⁵.</td>
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<td>Primary outcome</td>
<td>Overall survival.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Progression-free survival, time to progression, objective response rate, health related quality of life (measured using the European Organization for Research and Treatment of Cancer quality of life measurement [EORTC QLQ-C30], the HCC-specific questionnaire [HC-18], and EQ-5D-3L), pharmacokinetics, disease control rate, clinical benefit rate, exploratory biomarkers.</td>
</tr>
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<td>Expected reporting date</td>
<td>Estimated primary completion date reported as April 2016²¹.</td>
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ESTIMATED COST and IMPACT

COST

The company estimate the cost of lenvatinib per patient per year for the treatment of HCC at >£30,000¹.

Experts identified sorafenib as a suitable comparator to lenvatinib¹. Sorafenib is available at a cost of £2,980 for 112 200mg tablets²². The recommended dosage for hepatocellular carcinoma is 400mg twice daily, this would equate to a cost per patient per year of £38,846²².

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other
- No impact identified

¹ Modified Response Evaluation Criteria in Solid Tumours.
² Eastern Cooperative Oncology Group.
³ Company provided information.
⁴ Expert personal opinion.
### Impact on Health and Social Care Services
- Increased use of existing services
- Re-organisation of existing services
- Other
- Decreased use of existing services
- Need for new services
- None identified

### Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Other increase in costs
- Other
- Reduced drug treatment costs
- Other reduction in costs
- None identified: similar cost to sorafenib.

### Other Issues
- Clinical uncertainty or other research question identified: question about the place in treatment, evidence suggests a TKI is only a first line treatment in patients with good functional status and liver function with metastatic disease or large tumours with macrovascular involvement (situations where ablation or TACE provide no survival benefit). Lenvatinib could be used as a second or third line treatment for intermediate tumours that are not responding to/unsuitable for ablation or TACE in patients with good functional status and reasonable liver function\(^1\).
- None identified

### REFERENCES

\(^1\) Expert personal opinion.
12 NIHR Horizon Scanning Centre. Brivanib alaninate for hepatocellular cancer. University of Birmingham, February 2012. [www.hsric.nihr.ac.uk](http://www.hsric.nihr.ac.uk)


19 NIHR Horizon Scanning Centre. Doxorubicin-eluting beads (DC Bead, DC Bead M1 and Radiopaque DC Bead) for hepatocellular carcinoma. University of Birmingham, January 2016. [www.hsric.nihr.ac.uk](http://www.hsric.nihr.ac.uk)

