Sorafenib (Nexavar) for hepatocellular carcinoma - adjuvant therapy

Target group
- Hepatocellular carcinoma (HCC) - adjuvant therapy following surgical resection or ablation.

Technology description
Sorafenib (Nexavar; BAY 43-9006) is a raf signalling pathway inhibitor with raf kinase inhibitor activity. It has a dual action that targets serine/threonine kinases along the RAF/MEK/ERK pathway and receptor tyrosine kinases, inhibiting (1) the raf cascade to prevent the downstream mediation of cell growth and proliferation, and (2) the VEGFR-2/3, PDGFR-βa signalling cascade to inhibit the activation of angiogenesis, thus acting on both tumour cell growth and tumour vasculature. Sorafenib is intended for use as adjuvant treatment in patients who have undergone surgical resection or local ablation. Sorafenib is administered orally at a dose of 400mg, twice daily.

Sorafenib is licensed and has received orphan designation in the EU for the treatment of HCC and advanced renal cell carcinoma for patients who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

Recognised adverse effects (≥10%) of sorafenib include: abnormal laboratory test results, gastrointestinal, respiratory tract and brain haemorrhage, lymphopenia, diarrhoea, hair loss, hand-foot syndrome, itching, hypophosphataemia, nausea, pain, hypertension, skin rashes, tiredness and vomiting1.

Sorafenib is currently in phase III development for advanced breast cancer, non-small-cell lung cancer, thyroid cancer and renal cancer (adjuvant treatment). It is also in phase II trials for acute myeloid leukaemia, colorectal cancer, ovarian cancer, head and neck cancer, gastric cancer and germ cell and embryonal neoplasms.

Innovation and/or advantages
If licensed, sorafenib will present a new treatment option for this patient group who, following surgery, currently receive no treatment until disease recurrence. Sorafenib is currently only offered for advanced metastatic HCC.

Developer
Bayer.

Availability, launch or marketing dates, and licensing plans
In phase III trials.

NHS or Government Priority Area
None identified

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1 VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor.
Relevant guidance

- NICE technology appraisal. Sorafenib for the treatment of advanced hepatocellular carcinoma. May 2010\(^2\).
- NICE interventional procedure guidance. Ex-vivo hepatic resection and reimplantation for liver cancer. April 2009\(^3\).
- NICE interventional procedure guidance. Microwave ablation of hepatocellular carcinoma. March 2007\(^4\).
- NICE interventional procedure guidance. Radiofrequency-assisted liver resection. February 2007\(^5\).
- NICE interventional procedure guidance. Laparoscopic liver resection. July 2005\(^6\).
- NICE interventional procedure guidance. Radiofrequency ablation of hepatocellular carcinoma. July 2003\(^7\).

Clinical need and burden of disease

Liver cancer is the 18\(^{th}\) most commonly diagnosed cancer in UK, with around 3,400 new cases diagnosed in 2007\(^8\). Approximately 1 in every 100 cancers diagnosed in the UK is a primary liver cancer\(^9\). HCC is the main type of primary liver cancer, accounting for about 85\% of cases\(^10\). Most cases of HCC are secondary to either a viral infection (hepatitis B or C) or cirrhosis\(^11\). The incidence of HCC has increased in recent years as a result of the prevalence of infection with hepatitis C virus. Unlike the majority of cancers, HCC has very well-defined risk factors, with 80\% of cases developing in cirrhotic livers\(^12\).

In England and Wales, 1,210 deaths due to HCC were registered in 2009\(^13\). In 2009-2010 there were 2,859 admissions for HCC in England, resulting in 19,491 bed days and 3,916 finished consultant episodes\(^14\) (ICD10 C22.0).

Existing comparators and treatments

The only curative option for HCC is surgery:

- Hepatic resection - the treatment of choice in non-cirrhotic patients, applicable in <18\% of cases\(^15\).
- Liver transplantation - often limited by the shortage of cadaveric donors, applicable in only around 5\% of patients\(^6\).

For the majority of patients, treatment intent is palliative rather than curative. However, no adjuvant or palliative treatments have been conclusively shown to prolong survival\(^15\). These treatment modalities include percutaneous ablation, chemoembolisation, radiofrequency ablation and systemic chemotherapy with drugs such as cisplatin, doxorubicin and mitomycin\(^15\).

Sorafenib is licensed for the treatment of HCC, but not recommended for the treatment of advanced HCC in patients for whom surgical or locoregional therapies have failed or are unsuitable\(^2\).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>STORM, NCT00692770, 12414, 2008-001087-36; adults; sorafenib vs placebo; phase III.</th>
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<td>Bayer.</td>
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### Status
Ongoing.

### Source of information
Trial registry.[16]

### Location
EU (inc UK), USA, Canada and other countries.

### Design
Randomised, placebo-controlled.

### Participants and schedule
n=1,115; adults; patients who have undergone surgical resection or local ablation of HCC with curative intent.
Randomised to sorafenib 400mg twice daily or placebo.

### Follow-up
Continuous treatment until disease recurrence, unacceptable toxicity or other criteria for withdrawal are met.

### Primary outcome
Recurrence free survival.

### Secondary outcome
Time to recurrence; overall survival; patient-reported outcome as assessed by FACT-Hep[^6] and EQ-5D[^7] questionnaires; biomarker evaluation.

### Expected reporting date
Estimated study completion date Q4 2014.

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### Estimated cost and cost impact
The cost of sorafenib for this indication is not yet known. The price for a pack of 112 x 200mg tablets is £2,980.47[^17]. The company estimate a cost of >£30,000 per patient per year.

### Claimed or potential impact – speculative

**Patients**
- ✔ Reduced mortality or increased length of survival
- ✔ Reduption in associated morbidity or improved quality of life for patients and/or carers
- □ Quicker, earlier or more accurate diagnosis or identification of disease
- □ Other:

**Services**
- □ Increased use
- □ Service organisation
- □ Staff requirements
- □ Decreased use
- □ Other:
  - ✔ None identified

**Costs**
- □ Increased unit cost compared to alternative
- ✔ New costs: new treatment option.
- □ Increased costs: more patients coming for treatment
- □ Savings:
- □ Increased costs: capital investment needed
- □ Other:

**Other issues**
- □ Clinical uncertainty or other research question identified:
  - ✔ None identified

### References

[^7]: EQ-5D - a standardised instrument for use as a measure of health outcome with five attributes: mobility, self-care, usual activity, pain/discomfort and anxiety/depression.

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