Single Technology Appraisal (STA) of sorafenib (Nexavar®) for the treatment of hepatocellular carcinoma (HCC)

14th January 2009

Please note confidential information has been removed from this document

Contents

List of appendices

Appendices are provided in a separate document; see file *Nexavar HCC_STA form appendices.doc*

List of abbreviations

A&E	Accident and Emergency
CEA	Cost Effectiveness Analysis
CI	Confidence Interval
CT	Computed Tomography
CUA	Cost Utility Analysis
DCR	Disease Control Rate
ECG	Electrocardiogram
GP	General Practitioner
HCC	Hepatocellular Carcinoma
HRG	Healthcare Resource Group
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
LOS	Length of Stay
mITT	Modified Intention to Treat
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
od	Once daily
OS	Overall Survival
PFS	Progression Free Survival
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RD	Risk Difference
RR	Relative Risk
RRR	Relative Risk Reduction
SD	Standard Deviation
SE	Standard Error
SG	Standard Gamble
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
TTP	Time to Progression
TTSP	Time to Symptomatic Progression
VAS	Visual Analogue Scale

Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Sorafenib (Nexavar®) is a multi-kinase inhibitor.

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Marketing authorisation was received for sorafenib in October 2007.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

Sorafenib is indicated for the treatment of hepatocellular carcinoma.

Sorafenib is also indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

The Summary of Product Characteristics is included as Appendix 1.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

The date of marketing authorisation coincided with the UK launch of sorafenib. The exact number of patients using sorafenib is unknown but estimated to be minimal.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Regulatory approval was sought through the EMEA centralised procedure, therefore approval throughout Europe will be the same as for the UK. Sorafenib has also been approved by the FDA and in over 40 countries worldwide.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

The SMC issued guidance in July 2008.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Oral 200mg film coated tablet
112 tablet pack

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended dose of sorafenib in adults is 400 mg twice daily (bd; equivalent to a total daily dose of 800 mg). Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The list price of a 112 200mg tablet pack is £2,980.47.

1.10 What is the setting for the use of the technology?

Sorafenib will be prescribed by an Oncologist/Liver Specialist.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other aspects of care beyond routine clinical practice need to be considered.

2. Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with advanced hepatocellular carcinoma whose disease is unsuitable for local or loco-regional curative therapy or has progressed after those types of therapy	Sorafenib is indicated for the treatment of hepatocellular carcinoma (Appendix 1), the main type of primary liver cancer. In April 2006, on account of the small number of cases and lack of alternative therapies in HCC, sorafenib was granted European and US orphan drug status. The decision problem addressed in the submission is the clinical benefit and cost-effectiveness of sorafenib as a treatment in those patients with advanced stage hepatocellular carcinoma disease who have failed or are unsuitable for surgical or locoregional therapies. There are approximately 2340 new cases of HCC diagnosed in England and Wales each year(1). Of these the population eligible for Nexavar is around 700(2).
Intervention	Sorafenib (Nexavar)	Sorafenib tosylate (Nexavar®), a multi-kinase inhibitor, is an oral therapy for HCC, targeting both tumour angiogenesis (vasculature) and tumour cell proliferation. Sorafenib is administered orally in the form of 200 mg film coated tablets. The recommended dose of sorafenib in adults is 400 mg twice daily (bd; equivalent to a total daily dose of 800 mg). Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.
Comparator(s)	Standard care which may include doxorubicin, cisplatin or biological agents, depending on performance status and severity	Sorafenib will be compared to best supportive care. Due to the underlying liver disease and lack of effective treatments, patients diagnosed with advanced HCC have a bleak prognosis. Sorafenib is the only treatment to have

		demonstrated a survival benefit in advanced HCC for over 30 years(3). No systemic agent has shown survival benefit versus placebo in HCC in more than 75 randomised controlled trials(4) and, in most cases, such treatments are associated with a high rate of side effects. As a result, there are no treatments, other than sorafenib, with FDA and/or EMEA approval for advanced HCC. Furthermore, because of the advanced nature of the disease, surgery is not a treatment option. Guidelines (BSG 2003)(5) recommend that systemic chemotherapy with standard agents have a poor response rate and should only be offered in the context of clinical trials of novel agents. Best supportive care is the most appropriate comparator for these patients. This is supported by various reviews(6;7), meta-analyses(8) and systematic reviews(4;8-11) published over the past decade which conclude that no anti-cancer treatment has clearly been identified as either a 'gold standard' or to demonstrably improve overall survival.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression free survival • Time to symptomatic progression • Tumour response • Health related quality of life • Adverse effects of treatment	The outcomes listed will be presented in the submission. Advanced HCC is a unique condition which poses methodological issues when evaluating the impact of new treatments on health related quality of life. Patients with hepatocellular carcinoma are heterogeneous, with a diverse range of underlying causes of cirrhosis, including hepatitis B, hepatitis C, alcoholism and haemochromatosis. In some patients, typically younger women, HCC may develop where cirrhosis is not present. Due to this diverse liver disease, it is particularly difficult to disentangle the effect of the advanced HCC, underlying liver disease and interventions on quality of life. More specifically, quality of life is likely to be affected by the symptoms of the underlying liver disease, including

		liver failure, irrespective of whether the tumour has stabilised or regressed. As a result, it is not possible to demonstrate the impact of treatments in advanced HCC on quality of life, and no robust and reliable utility data is available that separates out the effect of the primary liver cancer from the underlying liver disease causes.
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year. The time horizon for the economic evaluation should be sufficiently long so as to incorporate all the important costs and benefits related to the condition. Where the evidence allows, any likely dose adjustment during the treatment should be taken account of. Costs will be considered from and NHS and Personal and Social Services Perspective	The economic evaluation will be a cost effectiveness analysis, with the results presented as incremental cost per quality adjusted life year and life year gained. Taking this uniqueness of confounding co morbidities into consideration, the QALY would not be an appropriate outcome to measure the health benefit of patients with advanced HCC, therefore the cost per life years gained figures should also be given consideration. Due to the advanced nature of the disease, the model will be a lifetime model, consisting of three health states; non-progressive advanced disease, progressive disease, and death. The model will also consider dose adjustments during the treatment period. Costs will be considered from an NHS perspective.
Special considerations, including issues related to equity or equality ***Subgroups to be considered***	If the evidence permits, the appraisal will seek to identify subgroups of individuals for whom sorafenib may be particularly clinically and cost effective, for example by age, performance status or degree of underling cirrhosis. Guidance will only be issued in accordance with the marketing authorisation.	Patients with advanced HCC have a heterogeneous co morbidity profile that affects their prognosis, quality of life and treatment. Given that this is an end of life medicine, with small patient numbers, a demonstrable survival benefit and no alternative treatments, sorafenib should be considered under the End of Life Policy(12). Applying a single estimate of cost-effectiveness to the overall advanced HCC group of patients is unreliable because of the unique large variation in underlying

		disease (e.g. liver cirrhosis), rarely seen in other cancers, it is therefore of utmost importance to base decisions on patient sub-groups where the health and economic outcomes are most likely to vary considerably from the overall mean. It is acknowledged there is a high degree of variability around the point estimate of cost effectiveness due to the heterogeneous nature of the disease and the difficulty disentangling the underlying liver disease and treatment effects. For these reasons it would be appropriate to collect further evidence as recommended under the end of life scheme.

Section B

3 Executive summary

This submission concerns the use of sorafenib (Nexavar®), which is licensed for the treatment of hepatocellular carcinoma, the main type of primary liver cancer, and also the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy (see Appendix 1). The decision problem addressed in this submission is the clinical benefit and cost-effectiveness of sorafenib as a treatment in those patients with advanced stage hepatocellular carcinoma who have failed or are unsuitable for surgical or locoregional therapies.

Sorafenib

Sorafenib tosylate (Nexavar®) is an oral multi-kinase inhibitor targeting both tumour angiogenesis (vasculature) and tumour cell proliferation(13). Sorafenib simultaneously inhibits molecular components of the Raf-MEK-ERK signalling pathway, abrogating tumour growth and VEGFR-1, VEGFR-2, VEGFR-3 and PDGFR- ß , thus inhibiting neoangiogenesis(13). It has activity in targeting these two key pathways implicated in the molecular pathogenesis of hepatocellular carcinoma(14-16).

Sorafenib is an oral twice daily treatment for hepatocellular carcinoma. It is supplied as a film-coated tablet in packs of 112 tablets, with each tablet containing 200 mg of sorafenib. The recommended dose of sorafenib is 400 mg taken twice daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. The list price is £2980.47 per pack. Assuming a median duration of treatment of 23 weeks based on the SHARP study, this is equivalent to £15,220 per treatment course.

Hepatocellular Carcinoma: Current management and guidelines

Hepatocellular carcinoma (HCC), the dominant form of primary liver cancer, accounts for about 80-90% of liver cancer cases. In the UK, HCC is the 18th most common cancer(17), with about 2340 new cases diagnosed in England and Wales in 2005(1). The incidence of HCC may rise in Western countries over the next few years, probably as a direct result of the Hepatitis C virus (HCV) epidemic(5).

The primary risk factor for HCC is cirrhosis, most commonly due to Hepatitis B; Hepatitis C; and alcohol. Classic symptoms include weight loss, abdominal pain and the presence of a mass; the diagnosis is confirmed by blood tests (raised alpha-fetoprotein (AFP) levels), imaging (ultrasound, arteriography, CT or MRI scan), and liver biopsy. Choice of therapy depends on how advanced the disease is, and also on the severity of the underlying cirrhosis.

Less than 30% of patients are diagnosed in the early stages where liver tumours are more amenable to curative resection or transplantation. Some patients at later stages may be suitable for “loco-regional” treatments: ablation (radiofrequency ablation (RFA); percutaneous ethanol injection (PEI) or cryosurgery); (chemo)embolisation, and radiotherapy. For patients where surgical or loco-regional treatments have failed or are unsuitable, systemic therapy is the only active treatment option, although no treatment has ever been shown to improve overall survival in a randomised controlled trial. The prognosis for patients with advanced HCC is therefore bleak, with 5-year survival rates of <5%(18).

The uncertainty about best practice and treatment options for patients with advanced HCC is clearly highlighted by the lack of direction regarding specific therapy recommendations in guidelines produced prior to the introduction of sorafenib (see section 4.6).

UK guidelines for the diagnosis and treatment of HCC, commissioned by the British Society of Gastroenterology in 2003, do not specify a standard systemic therapy to be used in advanced HCC(5). The guidelines acknowledge the poor results obtained with current

systemic anti-cancer agents, recommending the use of novel agents within the context of clinical trials. Research undertaken by Bayer on the treatments used by UK clinicians suggest limited active options aside from clinical trials of new agents and chemotherapy. Where chemotherapy was used, single agent doxorubicin or doxorubicin-containing combination therapies were more frequently mentioned, however these are only suitable for a minority of patients and low overall response rates (10-15%) and the risks associated with its use often outweigh any short term benefits (19). With limited active options aside from clinical trials of new agents and chemotherapy(5), clinicians opt for best supportive care (BSC) as the most common patient management strategy(19). Consequently, there is a compelling clinical need for effective treatments in order to improve the outlook for these patients.

Since the regulatory approval of sorafenib, there has been a noticeable shift in opinion as to the standard systemic treatment in advanced inoperable HCC. Due to sorafenib being shown to prolong survival in this patient group, several guidelines and review papers(20), including the revised UK guidelines, which are currently in development(21) now include sorafenib as the standard of care systemic therapy for patients with advanced HCC for whom no potential curative option is available. No other pharmacological treatments are approved by the FDA and/or EMEA for advanced HCC.

Clinical Evidence

Conclusions from various reviews(6;7), meta-analyses(8) and systematic reviews(4;8-11) published over the past decade, conclude that no anti-cancer treatment has clearly been identified either as a 'gold standard', nor been shown demonstrably to improve overall survival vs. best supportive care (BSC). In such a situation it is justifiable, with new treatments, to compare active treatment with placebo or BSC alone as the control arm(7).

Doxorubicin is used in a minority of patients, but low overall response rates (10-15%) and the risks associated with its use often outweigh any short-term benefits, and clinicians usually opt for a best supportive care (BSC) approach instead. A systematic review which identified studies involving sorafenib, doxorubicin, placebo or BSC in advanced HCC, confirmed this and informed on the heterogeneity in terms of dosage and treatment regimens, study population characteristics and outcome measures(22). The doxorubicin trials are generally small, with methodological flaws (e.g. lack of intention to treat analysis) and the heterogeneity of the patient groups makes the true effects of doxorubicin difficult to determine or compare. Hence data was insufficient to support even an indirect comparison with doxorubicin within the submission.

The efficacy of sorafenib, an oral treatment taken every day for the treatment of advanced HCC, has been demonstrated in a large, multicentre, randomised placebo-controlled trial (SHARP)(3). Its efficacy is supported by results from a smaller RCT in Asia-Pacific patients(23) and a phase II uncontrolled study(24). The SHARP study involved in 602 patients which showed sorafenib significantly improved overall survival with a hazard ratio of 0.69 over best supportive care, representing a 44% increase in overall survival(3). The median survival increased from 34.4 weeks to 46.3 weeks.(3). The benefit of sorafenib over placebo is observed across established prognostic subgroups, supporting the broad applicability of the treatment in HCC patients. Furthermore, in the RCT sorafenib was shown to delay progression of HCC by prolonged stabilisation of disease when compared with placebo/BSC, as confirmed by improved time to progression (TTP) (24 vs. 12.3 weeks, p=0.000007).

These results are supported by the Asia-Pacific RCT in which sorafenib significantly prolonged overall survival compared to placebo (HR=0.69, p=0.04), representing a 44.9% increase in survival time. Median TTP was 12 weeks with sorafenib and 6 weeks with placebo (HR=0.57, p=0.000658). Results from the phase II study were consistent with those observed in the SHARP study (median overall survival 9 months [investigator-assessment], median TTP 5.5 months [by independent assessment]). In all studies sorafenib was concluded to have a manageable and acceptable safety profile, the most common side effects being diarrhoea and hand-foot skin reaction. In the SHARP study, sorafenib was effective and well tolerated regardless of ECOG Performance Status, degree of liver impairment and presence

or absence of vascular invasion or extrahepatic spread, as well as in patients with aetiologies of hepatitis C virus (HCV) infection or alcohol abuse(3).

Sorafenib, a multi-kinase inhibitor, is the first systemic agent in more than 75 randomised controlled trials over the past 30 years to be shown to significantly improve overall survival in advanced HCC compared to BSC alone(4;25).

Evidence of Cost Effectiveness

A systematic review of the cost effectiveness literature did not identify any published cost effectiveness studies relevant to the submission and therefore there is a requirement for a de novo economic evaluation.

An economic model was built to assess the incremental cost effectiveness of sorafenib compared to best supportive care, the most commonly used therapy in this population, based upon the results of the randomised placebo-controlled, international, multicentre phase III SHARP trial. A lifetime (14 year) Markov model was constructed which included three key states representing the disease; non progressive advanced disease, progressive disease and death. The model was populated using the SHARP trial data and extrapolating the 72-week data to the longer timeframe using a lognormal distribution. The model includes costs for drugs and medications, monitoring and adverse events, routine follow-up, hospitalisations and palliative care. Treatment patterns were obtained from expert opinion. Utilities were obtained by mapping the health related quality of life (HRQL) values from a disease specific instrument used within the clinical trial to time trade-off (TTO) utilities for selected health states in advanced HCC patients using a published algorithm. Health outcomes were measured in terms of life years (LYs) and quality adjusted life years (QALYs). Incremental cost-effectiveness ratios (ICERs) include cost per LY and cost per QALY. Findings for the ICERs are reported using a 3.5% discount rate. Sensitivity analyses were conducted using subpopulations from the trial and by altering key model inputs.

The key assumptions underlying the economic model are as follows:

- The phase III SHARP study is the largest and most relevant data source for the decision problem being addressed
- BSC is the most frequently used therapy in advanced HCC, i.e. the appropriate comparator to sorafenib
- TTP was based on the trial investigators' assessment as this was believed to be the best representation of clinical practice
- The time-to-progression and overall survival observed in the treatment and the placebo group over 72 weeks can be extrapolated to the desired time horizons, with the help of lognormal distribution;
- The rate of AEs is assumed to be constant over the time horizon; and
- The disutilities due to AEs are additive, i.e. can be estimated by subtracting the utility of a given health state with an AE from the utility of that health state without any AE
- Based on expert clinical opinion disutilities due to AEs are not included after progression to avoid double counting, as most of these events are accounted for with the utility value of progression.

Sorafenib is an effective orphan medicine which results in an additional 0.36 QALYs gained compared to BSC. The incremental life years gained is 0.51. The respective ICERs are £64,754 and £45,502. Sensitivity analyses have shown that the cost-effectiveness results are most sensitive to changes in survival, price and utility values. Due to the difficulties in disentangling the quality of life differences associated with treatment versus the underlying liver disease the results obtained from the incremental cost per LY gained analysis might better represent the cost effectiveness of sorafenib in advanced HCC.

The cost effectiveness of treating these patients may be larger than traditionally accepted thresholds. However advanced HCC is a unique condition which poses methodological issues when evaluating the impact of new treatments. Patients with HCC are heterogeneous, with a diverse range of underlying causes. Due to this diverse liver disease it is particularly

difficult to disentangle the effect of advanced HCC, underlying liver disease and interventions on the costs and quality of life, furthermore these do not take into account the poor prognosis and unmet need for patients diagnosed with advanced HCC and the significant impact in terms of the costs and quality of life effects on relatives and/or carers.

There will be approximately 1750 patients in England and Wales suffering from advanced HCC over the next 5 years who may be suitable for sorafenib according to projected market shares. These patients currently have no active treatment options. Active therapy in the form of sorafenib offers the potential to increase overall survival. With a very small patent population eligible for treatment, the budget impact of the treatment is relatively low and is unlikely to reach more than £29 million over the next 5 years.

Conclusion

Due to the underlying liver disease and lack of effective treatments, patients diagnosed with advanced HCC have a bleak prognosis, with 5-year survival rates of <5%(18). Patients with advanced stage disease who have failed or are unsuitable for surgery or loco-regional treatments have limited treatment options. No other pharmacological treatments are approved by the FDA and/or EMEA for advanced HCC and best supportive care is the most commonly used treatment for these patients. This is supported by various reviews(6;7) meta-analyses(8) and systematic reviews(5;9-11) published over the past decade which conclude that no anti-cancer treatment has clearly been identified as either a 'gold standard' or to demonstrably improve overall survival.

A consistent body of good quality clinical evidence has found that in comparison with best supportive care, the currently received standard treatment in the UK, sorafenib is statistically superior at improving overall survival. Sorafenib, a multi-kinase inhibitor, is the first systemic agent in more than 75 randomised controlled trials over the past 30 years to be shown to significantly improve overall survival in advanced HCC compared to BSC alone.

The economic modeling suggests that the incremental cost effectiveness ratio (ICER) of sorafenib compared to best supportive care is £64,754 per QALY and £45,502 per life year gained. The budget impact is relatively low and is not anticipated to exceed £29 million over the next 5 years.

Advanced HCC is a unique condition which poses methodological issues when evaluating the impact of new treatments. Patients with HCC are heterogeneous, with a diverse range of underlying causes. Due to this diverse liver disease it is particularly difficult to disentangle the effect of advanced HCC, underlying liver disease and interventions on the costs and quality of life. Given that this is an end of life medicine, with small patient numbers, a demonstrable survival benefit and no alternative treatments, sorafenib should be considered under the End of Life Policy. For the reasons outlined it is acknowledged there is a high degree of variability around the point estimate of cost effectiveness For these reasons it would be appropriate to collect further evidence as recommended under the end of life scheme.

4 Context

4.1 *Overview of disease*

Hepatocellular carcinoma (HCC) is the dominant form of primary liver cancer, accounting for about 80-90% of liver cancer cases(26). It is the third most common cause of cancer-related death worldwide, and most prevalent in Asia and Africa(17). In accordance with NICE's 'End of Life' policy criteria, HCC affects a small population of patients in the UK with about 2751 new cases of liver cancer diagnosed in England and Wales in 2005(1), this is approximately 2340 cases of HCC, a proportion of which will be eligible for sorafenib.

The primary risk factor for HCC is cirrhosis (the replacement of normal liver cells by fibrous scar tissue, with patches of tissue regeneration). Whilst cirrhosis can have many causes, it is most commonly due to Hepatitis B; Hepatitis C; and alcohol. Unlike most other cancers, the incidence of HCC is rising in Western countries, probably as a direct result of the Hepatitis C virus (HCV) epidemic(5). In the UK the incidence trend has increased from 2.5 to 3.9 per 100,000 persons between 1993 and 2005(1).

The classic symptoms of HCC include weight loss, abdominal pain and the presence of a mass; the diagnosis is confirmed by blood tests (raised alpha-fetoprotein (AFP) levels), imaging (ultrasound, arteriography, CT or MRI scan), and liver biopsy. The choice of therapy depends on how advanced the HCC is, and also on the severity of the underlying cirrhosis.

Unfortunately, there are often no specific symptoms, and less than 30% of patients are diagnosed in the early stages where liver tumours are considered more amenable to curative resection or transplantation. Some patients may be suitable for "loco-regional" treatments: ablation (radiofrequency ablation (RFA); percutaneous ethanol injection (PEI) or cryosurgery); (chemo)embolisation, and radiotherapy. For patients where surgical or loco-regional treatments have failed or are unsuitable (approximately 25-35% of HCC patients(2)), systemic therapy is the only active treatment option. Prior to sorafenib, no drug or regimen could be defined as the standard systemic treatment in advanced HCC as no treatment had ever been shown to demonstrably improve overall survival (OS) in a randomised controlled trial (RCT) (6;27).

Doxorubicin is used in a minority of patients, but low overall response rates (10-15%) and the risks associated with its use often outweigh any short-term benefits, and clinicians usually opt for a best supportive care (BSC) approach instead. Therefore, within the present therapeutic landscape, the prognosis for patients with advanced HCC is bleak, with 5-year survival rates of <5%(18). Consequently, there is a compelling clinical need for effective treatments in order to improve the outlook for these patients.

With the introduction of sorafenib, there has been a noticeable shift in opinion as to the standard systemic treatment in advanced inoperable HCC. Due to sorafenib being shown to prolong survival in this patient group, several guidelines and review papers(20), including the revised UK guidelines(21) (as yet unpublished) now include sorafenib as the standard of care systemic therapy for patients with advanced HCC for whom no potential curative option is available.

4.2 *Rationale for development of the technology*

Sorafenib's potential to inhibit the RAF/MEK/ERK pathway and the VEGFR-2 and PDGFR- ß receptors was a significant element of the rationale for studying its clinical effects in HCC(28). Preclinical models demonstrate that the RAF/MEK/ERK pathway has a role in HCC(29). RAF is over-expressed in a high percentage of human HCC tumours, and it has been shown that the RAF/MEK/ERK pathway can be activated by the major HCC aetiologic factors HBV and HCV(30). Phase I study results in solid tumours were suggestive of a therapeutic effect in HCC(31) and led to the design of a phase II study(24). In April 2006, on account of the small number of cases and lack of alternative therapies in HCC, sorafenib (Nexavar) was granted European and US orphan drug status. Subsequently, the safety and efficacy of sorafenib in advanced HCC was demonstrated in the pivotal phase III SHARP study: a multicentre double

blind placebo controlled trial in 602 patients which showed sorafenib significantly improved overall survival with a hazard ratio of 0.69 over best supportive care, representing a 44% increase in overall survival(3). This equated with the survival increasing from 34.4 weeks to 46.3 weeks(3).

4.3 *Principal mechanism of action of sorafenib*

Sorafenib tosylate (Nexavar®),a multi-kinase inhibitor, is an oral therapy for HCC, targeting both tumour angiogenesis (vasculature) and tumour cell proliferation(13). Sorafenib inhibits the signalling kinase RAF, and the receptor kinases VEGFR-2, VEGFR-3, PDGFR-ß, c-KIT, FLT-3 and RET(32)(Nexavar SmPC – Appendix 1). Sorafenib simultaneously inhibits molecular components of the Raf-MEK-ERK signalling pathway, abrogating tumour growth and VEGFR-1, VEGFR-2, VEGFR-3 and PDGFR- ß, thus inhibiting neoangiogenesis(13). It has activity in targeting these two key pathways implicated in the molecular pathogenesis of hepatocellular carcinoma(14-16).

4.4 *Suggested place with respect to currently available treatments for advanced HCC*

It is anticipated that sorafenib will become the standard systemic therapy for advanced hepatocellular carcinoma. There are no other treatments with FDA or EMEA approval for advanced HCC.

For patients where surgical or loco-regional treatments have failed or are unsuitable, systemic therapy is the only active treatment option. Prior to the study of sorafenib in HCC, no treatment had been shown to improve overall survival (OS) in a randomised controlled trial (RCT). This is supported by conclusions from various reviews and guidelines(6;7;27), meta-analyses(8) and systematic reviews(4;8-11) published over the past decade, where no anti-cancer treatment was identified as a ‘gold standard’.

UK guidelines for the diagnosis and treatment of HCC, commissioned by the British Society of Gastroenterology in 2003, do not specify a standard systemic therapy to be used in advanced HCC(5). The guidelines acknowledge the poor results obtained with current systemic anti-cancer agents, recommending the use of novel agents within the context of clinical trials.

Research undertaken by Bayer on the treatments used by UK clinicians suggest limited active options aside from clinical trials of new agents and chemotherapy in advanced HCC patients who are unsuitable for surgery, chemoembolisation or radiofrequency ablation (RFA). Where chemotherapy was used, single agent doxorubicin or doxorubicin-containing combination therapies were more frequently mentioned, however these are only suitable for a minority of patients(19). Doxorubicin produces low overall response rates (10-15%) and the risks associated with its use often outweigh any short-term benefits, and clinicians usually opt for a best supportive care (BSC) approach instead.

4.5 *Issues relating to current clinical practice*

A systematic review of the literature, prior to the introduction of sorafenib, suggested that no anti-cancer treatment had been clearly identified as the treatment of choice in this advanced, inoperable patient group(22). Best supportive care (BSC) is the most common patient management strategy. Hence placebo / BSC is justified as being a relevant comparator arm in studies evaluating novel agents such as sorafenib for the treatment of HCC(7).

Studies involving doxorubicin, placebo or BSC, identified during the systematic review, confirmed the lack of clarity on standard treatment and the heterogeneity in terms of dosage and treatment regimens, study population characteristics and outcome measures. Although doxorubicin may be used in a small number of patients, it’s use is not supported by current guidelines and data identified in the systematic review(22) was insufficient to support even an indirect comparison. The doxorubicin trials are small, with methodological flaws (e.g. lack of intention to treat analysis) and the heterogeneity of the patient groups makes the true effects of doxorubicin difficult to determine.

The uncertainty about best practice and treatment options for patients with inoperable advanced HCC is clearly highlighted by the lack of direction regarding specific therapy recommendations in guidelines produced prior to the introduction of sorafenib (see section 4.6).

Since sorafenib approval, there has also been a noticeable shift in opinion as to the standard systemic treatment in advanced inoperable HCC. Due to sorafenib being shown to prolong survival in this patient group, several guidelines and review papers(20), including the revised UK guidelines(21) (as yet unpublished) now include sorafenib as the standard of care systemic therapy for patients with advanced HCC for whom no potential curative option is available.

4.6 *Relevant guidelines or protocols*

British Society for Gastroenterology(5)
Guidelines for the diagnosis and treatment of Hepatocellular Carcinoma (HCC) in adults, 2003.

Recommendation on systemic treatments (section 4.3):

- Systemic chemotherapy with standard agents has a poor response rate and should only be offered in the context of trials of novel agents (evidence grade I, recommendation grade A)

> *"Chemotherapy given intravenously has a very limited role in the treatment of HCC. The best single agent is doxorubicin with response rates of 10–15%. More aggressive combination chemotherapy regimens show no improvement in response rates and may even produce a reduction in survival of treated patients. Any agents used in HCC should be given in the context of clinical trials."*

These guidelines are currently being updated. A draft form of the revised guidelines has been provided to us which includes the following revision on the 2003 guideline(21):

> *"Sorafenib has been shown to prolong survival in patients with advanced HCC and is the standard of care for patients with advanced HCC for whom no potential curative option is available (evidence 1b, recommendation grade A).*
>
> *Systemic chemotherapy with standard agents has a poor response rate (evidence grade I, recommendation grade A) but can be offered where no alternative therapy is available."*

Scottish Medicine's Consortium
Sorafenib (July 2008)(33)

Sorafenib is not recommended for use within NHS Scotland for the treatment of hepatocellular carcinoma. In one trial in patients with advanced hepatocellular carcinoma, sorafenib was superior to placebo in terms of overall survival, but not for the time to symptomatic progression. The manufacturer's justification of the treatment's cost in relation to its benefit was not sufficient to gain acceptance by SMC.

Scottish Intercollegiate Guidelines Network (SIGN): No existing guidance

American Association for the Study of Liver Diseases (AASLD)
AASLD Practice Guideline. Management of Hepatocellular Carcinoma, 2005(27)

> "*Systemic chemotherapy with any of the available agents has marginal anti-tumor activity and no impact on survival. Despite this lack of efficacy and the associated morbidity, chemotherapy (usually doxorubicin) is frequently administered in conventional clinical practice. Furthermore, it is also sometimes used as a control arm in some research studies. This policy must be discouraged, since if a treatment is thought to be inactive and used as a placebo, it should at least be non-toxic and easy*

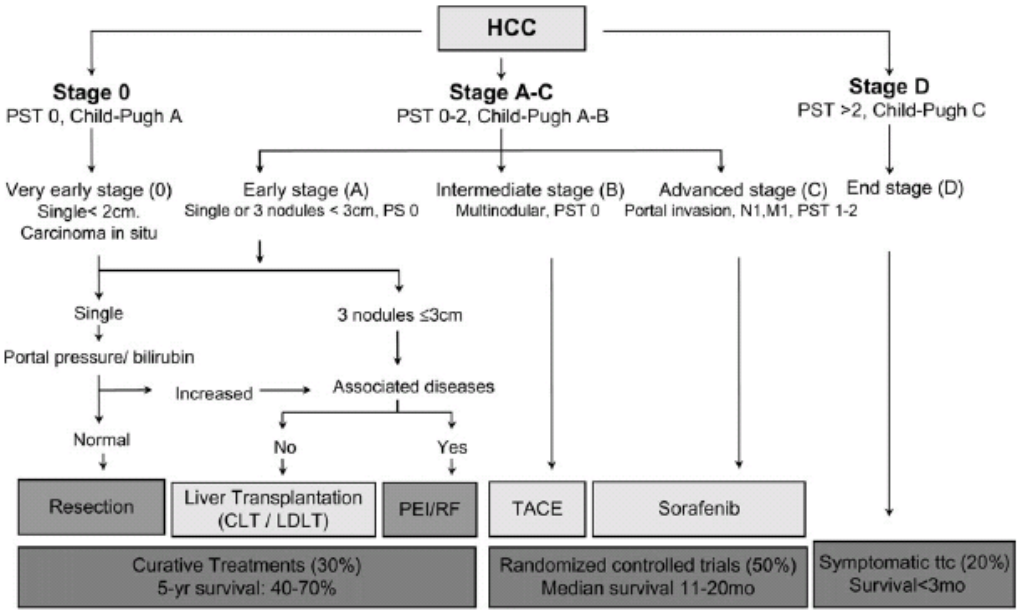
to administer. In fact, in the absence of effective therapy, the goal of health care providers should be to avoid unnecessary suffering with impairment of quality of life."

National Comprehensive Cancer Network (NCCN) (US)
NCCN Clinical Practice Guidelines in Oncology Hepatobiliary Cancers V.2. 2008(20)

The only specific recommended systemic therapy is sorafenib:

> *<u>Patients with unresectable and inoperable disease or those that decline surgery.</u>*
> *Alternative therapies …include sorafenib (Child Pugh A or B), clinical trial, ablative therapy (e.g. radiofrequency, alcohol, cryotherapy, microwave), chemoembolisation, chemotherapy plus radiation in a clinical trial, conformal radiation, radiotherapeutic microspheres, supportive care, and systemic or intra-arterial chemotherapy in a clinical trial.*

Treatment by BCLC staging(34) (adapted from Llovet et al 2003)(35)



5 Equity and equality

5.1 *Identification of equity and equalities issues*

Prior to the introduction of sorafenib for advanced inoperable HCC there was no recognised standard therapy. Advanced inoperable HCC is an incurable condition from which there have previously been few opportunities for respite and delay of inevitable death, even for a few months. Patients who have failed or who are unsuitable for surgical or loco-regional therapies have a poor prognosis. If left untreated these patients would only have 3-6 months to live. Sorafenib significantly prolongs survival by 44% (HR=0.698; p=0.00058) (versus best supportive care) and delays progression of disease and does so with a manageable toxicity profile.

This is a relatively rare cancer in the UK and there is a high unmet and urgent clinical need for effective treatment within this patient group.

Patients with advanced HCC have a heterogeneous co morbidity profile that affects their prognosis, quality of life and treatment. Given that this is an end of life medicine, with small patient numbers, a demonstrable survival benefit and no alternative treatments, Nexavar should be considered under the End of Life Policy(12).

Applying a single estimate of cost-effectiveness to the overall advanced HCC group of patients is unreliable because of the unique large variation in underlying disease (e.g. liver cirrhosis), rarely seen in other cancers, it is therefore of utmost importance to base decisions on patient sub-groups where the health and economic outcomes are most likely to vary considerably from the overall mean.

It is acknowledged there is a high degree of variability around the point estimate of cost effectiveness due to the heterogeneous nature of the disease and the difficulty disentangling the underlying liver disease and treatment effects. For these reasons it would be appropriate to collect further evidence as recommended under the end of life scheme.

As highlighted, during the scoping of this technology, it is thought that the incidence of HCC will increase in the next few years mainly as a result of the rising prevalence of hepatitis C and hepatitis B virus infections. It is therefore important to ensure equality of treatments across all subgroups where similar clinical benefit has been observed.

No other issues relating to equity or equalities were identified.

5.2 *How has the analysis addressed these issues?*

Not applicable

6 Clinical evidence

6.1 *Identification of studies*

A systematic review was undertaken to identify all literature relating to systemic anti-cancer therapies in advanced hepatocellular carcinoma (HCC)(22). The search strategy specifically aimed to identify all studies comparing sorafenib with either an active control or placebo. It was anticipated that there would be very few studies so the search was kept intentionally broad to highlight uncontrolled studies also. An additional focus of the searches was to review available data on all studies involving either doxorubicin, placebo or best supportive care (BSC) as a 'systemic treatment' arm for advanced HCC. This was done in order to inform on the most appropriate comparators to use in the economic assessments, and also assess the quality of this data for any meta-analysis or indirect comparisons in the clinical and economic sections.

Due to the generally poor response rates produced by systemic chemotherapy in HCC, there was no clear indication from the literature of a 'gold standard' - in fact, the majority of publications over the last 4 years report on early exploratory studies with new agents. The UK guidelines, produced in 2003, suggest doxorubicin as the best chemotherapeutic agent in the treatment of HCC with response rates of 10-15%(5). However, the scoping search did not identify any published trials comparing sorafenib, as a single agent, with doxorubicin. Placebo-controlled trials and trials comparing doxorubicin with other chemotherapies were thus included in the search, in order to allow for any later decisions to do indirect comparisons between sorafenib and other relevant treatments to the UK. Review papers on anti-cancer therapies highlight that no drug or regimen could be defined as the standard treatment in advanced HCC and hence best supportive care / placebo may be the most appropriate comparator(6). This was supported by the American Association for the Study of Liver Diseases (AASLD) Practice guidelines in 2005(27).

Four electronic bibliographic databases were searched, covering biomedical, science and health economic literature (Medline, Embase, The Cochrane Library including NHS EED, and Health Economic and Evaluations Database (HEED)).

Additional studies were identified in a search of abstracts from key Oncology conferences (American Society of Clinical Oncology (ASCO), European Cancer Conference (ECCO)ASCO, ECCO). Also the reference lists of relevant articles identified in the database searches were hand-searched.

Further information on the databases searched, inclusion and exclusion criteria and search strategies can be found in Appendix 2 (section 10.2). Details of the cost-effectiveness literature search can be found in Section 7 and Appendix 3 (section 10.3).

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the inclusion / exclusion criteria set out in section 6.2.2. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Where available the following data were reviewed: Baseline characteristics, Overall Survival, Time to Symptomatic Progression, Time to progression, Progression-free survival, Response rate (including complete and partial response), adverse events, Health-related quality of life and costs from all reported perspectives.

6.2 *Study selection*

6.2.1 Complete list of RCTs

Two studies compare single-agent sorafenib with placebo(3;23). At the time of the systematic review the Asian-Pacific study was published only in abstract form(23), while the SHARP study(3), had been analysed and fully published. Since then the Asian-Pacific study has been published on-line (17th December 2008)(36).

Table 1: RCTs involving sorafenib as a single-agent identified during the systematic review

Author	Study Title	No of patients / Interventions
Llovet 2008(3), ASCO abstract 2007(25)	A Phase III randomised, placebo-controlled study of sorafenib in patients with advanced hepatocellular carcinoma *[also known as the SHARP (Sorafenib HCC Assessment Randomised Protocol) study]*	n=602 Sorafenib 400mg bd n=299 vs placebo n=303
Cheng 2008(23;36)	Randomised phase III trial of sorafenib versus placebo in Asian patients with advanced hepatocellular carcinoma (Study 11849 Asia Pacific trial)	n=226 Sorafenib 400mg bd n=150 vs placebo n=76

6.2.2 Inclusion and exclusion criteria

Included: Randomised, controlled trials (RCTs) comparing sorafenib as a single agent with other therapies (including placebo), involving patients aged 18 with a diagnosis of advanced inoperable HCC. Patients were to have had no prior *systemic* therapy (as this was one of the inclusion criteria for the phase III SHARP trial).

Excluded: Phase I studies, open-label studies, dose-ranging studies, non-English language references, trials involving intra-arterial agents or Transarterial embolisation (TAE) and Transarterial Chemo-embolisation (TACE) studies were excluded.

See 10.2.6 for list of full inclusion and exclusion criteria for the overall search.

6.2.3 List of relevant RCTs

Table 2: Relevant RCTs involving sorafenib as a single-agent identified during the systematic review

Author	Study Title	No of patients / Interventions
Llovet 2008(3), ASCO abstract 2007(25)	A Phase III randomised, placebo-controlled study of sorafenib in patients with advanced hepatocellular carcinoma *[also known as the SHARP (Sorafenib HCC Assessment Randomised Protocol) study]*	n=602 Sorafenib 400mg bd n=299 vs placebo n=303

The SHARP study(3;28), which has been analysed and fully published will provide the evidence for the clinical effectiveness of sorafenib in HCC in this submission. The Asian-Pacific study (Cheng 2008)(23;36) will be provided as supporting data because this is based on a different patient population with different underlying characteristics and aetiologies.

6.2.4 List of relevant non-randomised controlled trials

One phase II study examines the use of sorafenib in an open multicentre study(24;37) and will be used where appropriate to support the SHARP study results.

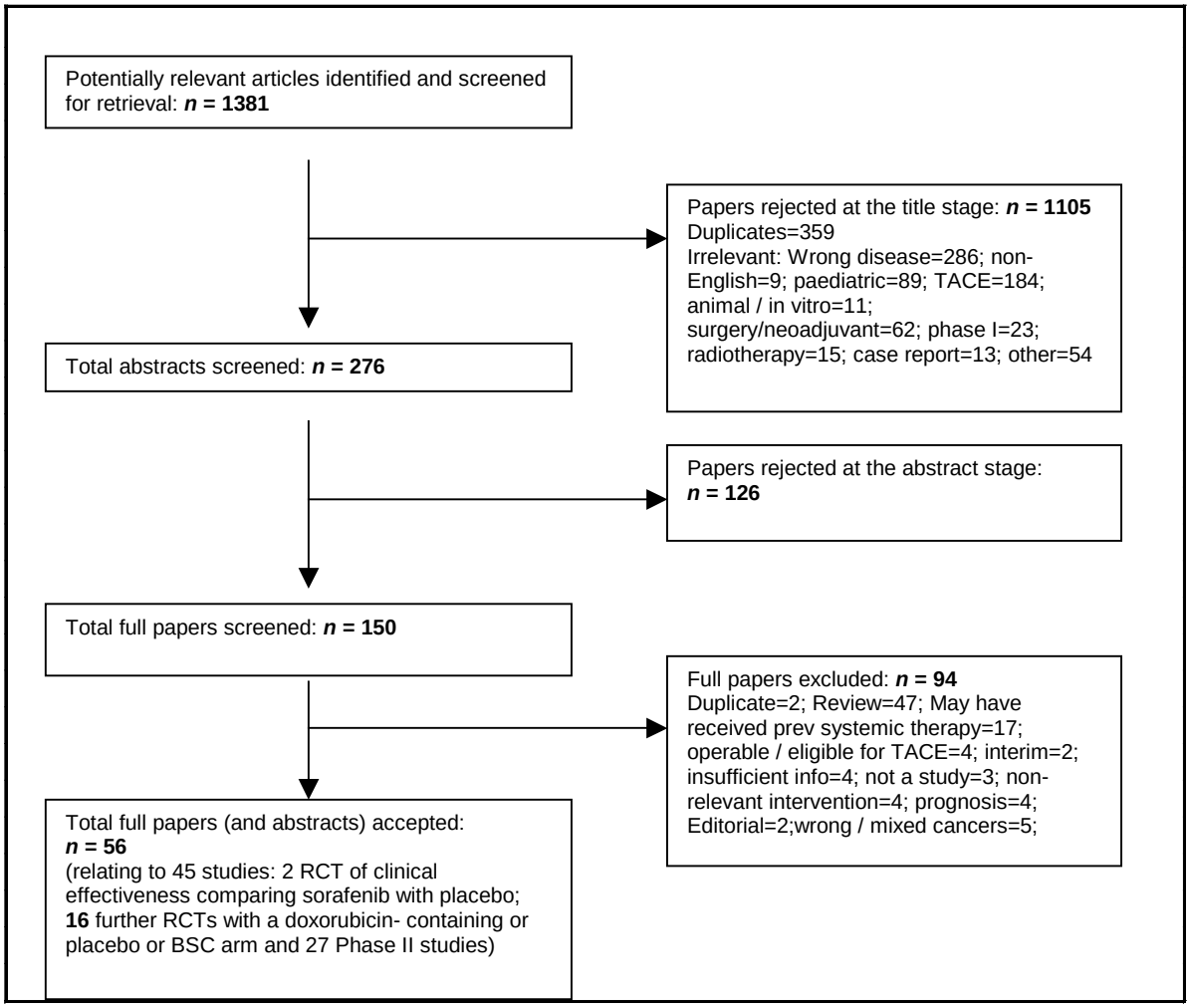
6.2.5 Ongoing studies

A search of the National Cancer Institute's (NCI) Clinical Trials' database (http://www.cancer.gov/clinicaltrials/search Accessed on November 29th 2008) has identified a total of 6 studies with sorafenib in HCC, relevant to the decision problem.

Table 3: Ongoing studies involving sorafenib in HCC

Title	Arm A	Arm B	Expected Accrual	Status	Data source
Phase IV					
GIDEON – Post Marketing Surveillance Study in HCC	Sorafenib		3000	Ongoing Expected closure September 2013	NCI / Bayer
Phase III					
Sunitinib vs sorafenib in patients with inoperable liver cancer	Sorafenib	Sunitinib	1200	Ongoing Expected closure July 2012	NCI
Study 11721 Phase III Study of BAY 43-9006 in Patients With Advanced Hepatocellular Carcinoma Treated After TACE (Japan)	Sorafenib	Placebo	414	Ongoing Expected closure March 2010	NCI / Bayer
Phase II					
Study 11546 A randomised controlled study of BAY 43-9006 in combination with doxorubicin versus doxorubicin in patients with advanced hepatocellular carcinoma.	Sorafenib + doxorubicin	Doxorubicin	96	Closed	NCI
Dose Escalation of Sorafenib in Patients With Advanced HCC (Italy)	Sorafenib	-	100	Ongoing	NCI
Phase I & unspecified					
Sorafenib in locally advanced or metastatic liver cancer with Child B cirrhosis	Sorafenib	-	30	Ongoing Expected closure September 2010	NCI

Figure 1 Flow Chart of the Clinical evidence screening process for sorafenib in inoperable advanced HCC



6.3 *Summary of methodology of relevant RCTs*

6.3.1 Methods

Trial Design(3;28)
The SHARP study was an international randomised, double-blind, placebo-controlled, multicentre phase III study designed to evaluate the clinical benefits of sorafenib versus placebo in advanced HCC. Patients were classified as having advanced disease if they were not eligible for, or progressed after, surgical or locoregional therapies. This study underwent Special Protocol Assessment with the Food and Drug Administration (FDA) which supported the use of a placebo control arm. The use of placebo as a comparator was also endorsed by the European Agency for the Evaluation of Medicinal Products (EMEA) in a Committee for the Medicinal Products for Human Use (CHMP) scientific advice letter dated 31 August 2004(38).

Enrolment into the study started in March 2005 and was completed in April 2006, during which time 902 patients had been screened and, following a screening period of up to 28 days, 602 patients subsequently randomised to treatment. Patients from 121 centres across 21 countries from Europe, North America, South America, and Australasia were randomised in a ratio of 1:1 to receive either sorafenib (400mg bd) or matching placebo orally every day.

A computer-generated randomisation list was prepared by Bayer, using a unicentric randomisation scheme. The randomisation number for each patient was provided through a telephone Interactive Voice Response System (IVRS). Randomisation was stratified by:

- "Tumour burden" (presence or absence of macroscopic vascular invasion and/or extrahepatic spread and describes an aggressive and advanced tumour pattern)
- ECOG PS of 0 versus 1 versus 2 (see Appendix 4)
- Geographical region (North America versus South America [including Mexico] versus Europe [including Australia/New Zealand])

Placebo was identical in appearance and delivered under identical conditions and dosing regimen to active treatment in order to preserve blinding. Study medication was labelled with a unique number, assigned to the patient via IVRS. These codes were kept within individual sealed envelopes. This process meant that, in the event of an emergency study medication, could be identified for an individual person without jeopardising the double-blind integrity of the remainder of the study patients.

Study treatment was administered orally on a continuous basis but for the purposes of data recording, the treatment period was divided into 6-week cycles. Study visits occurred every 3 weeks during treatment for evaluation of safety and drug accountability. Treatment continued until radiological and symptomatic progression, death, or adverse events required discontinuation of study treatment or withdrawal from the study, or until another criterion for stopping therapy was met (eg deterioration of PS to 4, development of second cancer).

At days 21-35 after the last dose of study medication, an 'end of treatment' visit was performed. Patients then entered a follow-up period whereby information on survival status and any new anti-cancer treatment was collected every 3 months.

At the second interim analysis, sorafenib was found to significantly prolong survival, which meant that all patients ongoing in the double-blind phase, as well as patients in follow-up were unblinded and given the opportunity to enter into an 'extension with crossover' study phase, provided the investigator deemed benefit could be derived from sorafenib treatment, there were no safety concerns in restarting treatment, and that informed consent was obtained. The primary objective of this phase was to make sorafenib available to all randomised patients. Additional safety data only were collected during this phase.

Study interventions
Patients entered into the SHARP study received either 400mg of sorafenib twice daily or placebo twice a day. Medication was taken orally and on a continuous daily basis until disease progression, death or withdrawal from the study for other reasons.

Dose reductions were permitted to predefined levels of 400mg once daily and subsequently to 400mg every 2 days for adverse events related to study interventions.

Treatment compliance
Compliance was assessed on the basis of pill counts and diary entries of patients.

Concomitant medications
All patients could receive best supportive / palliative care while participating in the study and all medication considered necessary for a patient's welfare, which was not expected to interfere with evaluation of sorafenib, was permitted. This included non-conventional therapies such as herbs, acupuncture, vitamins and mineral supplements, bisphosphonates for bone metastases, chronic erythropoietin, analgesics, nutritional support and palliative radiotherapy for local pain control.

Excluded medications were rifampicin, St. John's Wort, bone marrow transplant or stem cell rescue, other investigational or anti-cancer therapies, bevacizumab and other VEGF or VEGF receptor inhibitors, immunotherapy, hormonal therapy (including megestrol acetate or medroxyprogesterone), or molecular therapy.

Patients taking narrow therapeutic index medications, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporin and digoxin, were monitored. All concomitant medications (start/stop dates, dose, administration route, indication) were recorded for each participant.

6.3.2 Participants

Population under study (Inclusion & Exclusion criteria)(3;28)

Included: Patients with advanced measurable HCC ineligible for or had disease progression after surgery or loco-regional treatment, no prior systemic treatment, ECOG PS 0-2 (see Appendix 4) and Child-Pugh status A (see Appendix 5). Aged>18; Patients were required to have a life expectancy of at least 12 weeks and to have given written consent prior to any study-specific screening procedures. Patients had to have at least one tumour lesion that could be accurately measured in at least one dimension according to RECIST (Response Evaluation Criteria in Solid Tumours) (see Appendix 6) and the same tumour lesion must not have been previously treated with local therapy. Local therapies were defined as surgery, radiation therapy, hepatic arterial therapy, chemoembolisation, radiofrequency ablation, percutaneous ethanol injection or cryoablation. Patients could have been treated with such local therapies for other tumour lesions; however local therapy must have been completed at least 4 weeks prior to baseline scan.

Patients were required to have adequate haematologic function (platelet count >60x10^9/L; Haemoglobin >8.5g/dL; Prothrombin time (PT)-international normalised ratio (INR)<2.3 or PT<6 seconds above control); Adequate hepatic function (albumin >2.8g/dl; Total bilirubin <3mg/dL; Alanine transaminase (ALT) and aspartate aminotransferase (AST) <5xupper limit of normal (ULN)), Adequate renal function (serum creatinine <1.5xULN); albumin > 2.8g/dl; Amylase and lipase < 1.5 x ULN;

Excluded: Any patients who had received prior *systemic* anti-cancer therapy were excluded. Also excluded were patients with previous or concurrent cancer distinct from HCC *except* cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumours (Ta,Tis & T1) or any cancer curatively treated > 3 years prior to entry into the study. Other exclusion criteria were: a history of cardiac disease (congestive heart failure > New York Heart Association (NYHA) class 2, active coronary disease (CAD), cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin or uncontrolled hypertension);

renal failure requiring haemo- or peritoneal dialysis; active clinically serious infections (i.e. NCI grade > 2, CTCAE version 3(39)); known history of human immunodeficiency virus (HIV) infection; known central nervous system tumours including metastatic brain disease; clinically significant gastrointestinal bleeding within 30 days prior to study entry; history of organ allograft; substance abuse, medical psychological or social conditions that may have interfered with the subject's participation or evaluation of study results; known or suspected allergy to sorafenib or other agents given in association with the SHARP study; inability to swallow oral medications; pregnancy or breast-feeding. Any condition that was unstable or could have jepoardised the safety of the subject and his / her compliance in the study. Any patients who had Previously received molecular targeted therapies or any other systemic treatment.

Patient characteristics at baseline(3;28)
Of the 602 patients randomised and valid for inclusion in the ITT population, 524 were men (n=264 [87%] placebo; n=260 [87%] sorafenib), 534 were Caucasian (n=273 placebo; n=261 sorafenib) and 370 were 65 years of age or older (n=195 placebo; n=175 sorafenib). The median age was 66 years (placebo) and 65 years (sorafenib). Eighty seven per cent of the placebo patients (n=263) were from 'Europe & Australasia' as were 88% (n=263) of the sorafenib patients (see Table 4).

At baseline, 325 patients (54%) had an ECOG PS of 0 (n=164 [54%] placebo; n= 161 [54%]) and 277 patients an ECOG PS of 1 or 2 (n=139 placebo; n=138 sorafenib). Tumour burden, defined as presence of macroscopic vascular invasion and/or extra hepatic spread, was present in 421 patients (n=212 placebo; n=209 sorafenib). The majority of patients were Child-Pugh class A (n=297 placebo; n=284 sorafenib). Liver cirrhosis was confirmed by histological or clinical criteria in 219 placebo and 210 sorafenib patients and the most frequent aetiology of underlying liver disease was hepatitis C (n=82 placebo; n=87 sorafenib) followed by alcohol (n=80 placebo; n=79 sorafenib) and hepatitis B (n=55 placebo; n=56 sorafenib). The majority of patients had progressive disease at the time of randomisation and almost half (48.8%) had Tumour node metastases (TNM) Stage IV disease at that time.

There were no meaningful differences between the 2 treatment groups with respect to demographic or baseline characteristics. Median time from initial diagnosis to randomisation was 0.4 years (range 0 – 9.2 years).

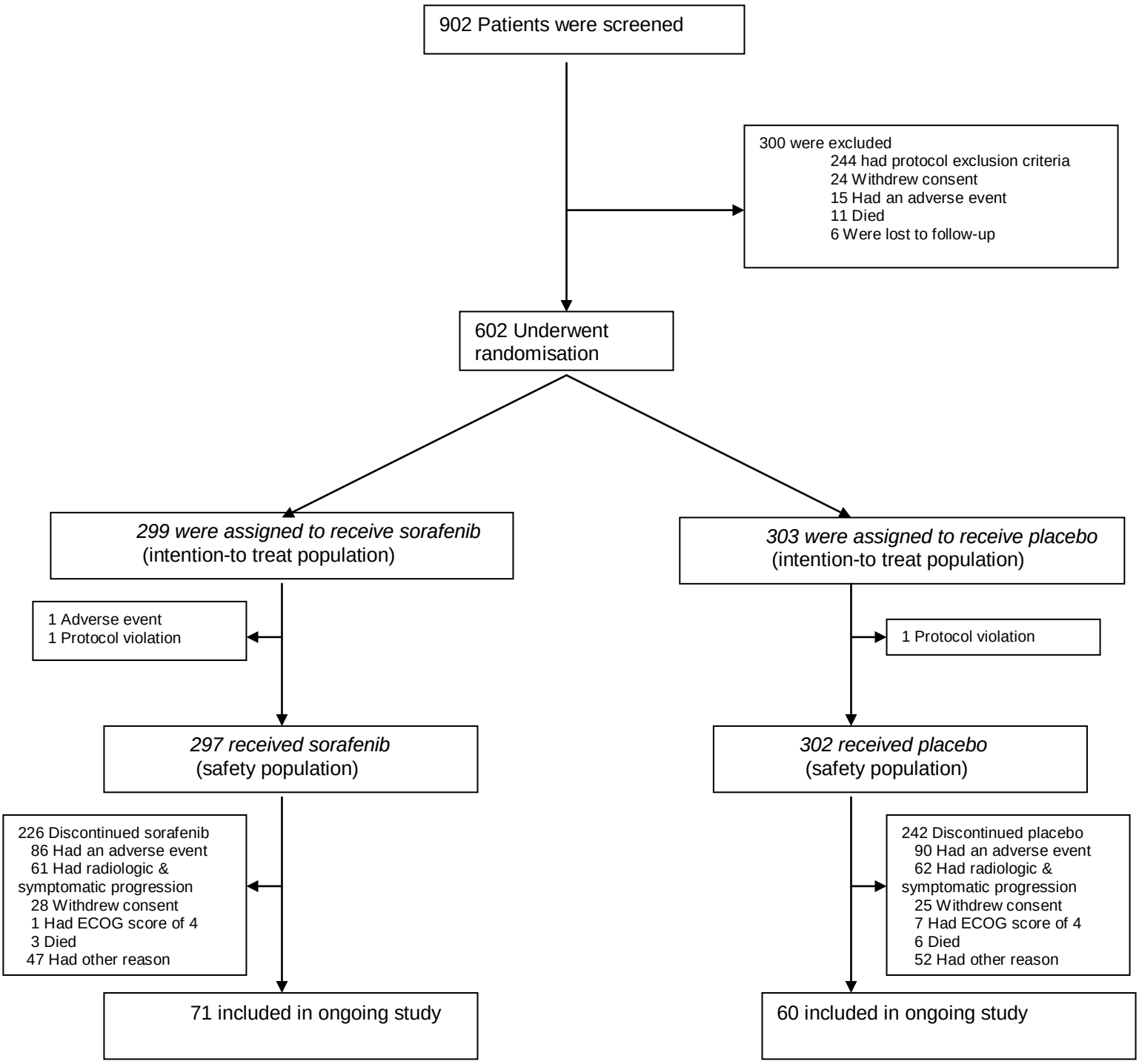
Table 4: Baseline characteristics of the SHARP study population

	Population	Treatment arm described here	Male:Female (%)	Median age (range)	T bilirubin µmol/l (range)	Albumin g/l (range)	ALP IU/L	AST (or SGOT) IU/L	AFP ng/ml (range)	ECOG performance status 0/1/2/3 (%)	BCLC stage Stage B / Stage C (%)
SHARP study (2008) (3;28)	European, N & S American, Australia / New Zealand, Israel, Russia	Sorafenib n=299 Placebo n=303	Sorafenib 87:13 Placebo 87:13	Sorafenib 67 Placebo 68 Mean±SD Sorafenib 64.9±11.2 Placebo 66.3±10.2	mg/dL Sorafenib 0.7 (0.1-16.4)) Placebo 0.7 (0.2-6.1) Mean+SD Sorafenib 1.0+1.4 Placebo 0.9+0.7	g/dL Sorafenib 3.9 (2.7-5.3) Placebo 4.0 (2.5-5.1) Mean+SD Sorafenib 3.9+0.4 Placebo 4.0+0.4	Sorafenib 149 (55-1924) Placebo 156 (42-1428) Mean+SD Sorafenib 203+167.9 Placebo 207.9+171.4	Sorafenib 62 (15-308) Placebo 60 (15-348) Mean+SD Sorafenib 73.2+44.7 Placebo 76.2+51.1	Sorafenib 44.3 (0-2,080,000) Placebo 99 (0-500,000)	Sorafenib 161/114/24 (54/38/8%) Placebo 164/117/22 (54/39/7%)	Sorafenib 54 / 244 (18 / 82) Placebo 51 / 252 (17 / 83)

	HBsAg positive % (HbeAg positive %)	Anti HCV positive or Hepatitis C positive %	Alcohol abuse %	Coexisting Cirrhosis %	Stage Limited to Liver vs Distant metastases (%)	Vascular involvement or portal vein invasion / thrombosis %	Child Pugh grading A/B/C (%)
SHARP study (2008) (3;28)	Sorafenib n=56 (19%) Placebo N=55 (18%) NB other patients may have had Hepatitis B & C	Sorafenib n=87 (29%) Placebo n=82 (27%) NB other patients may have had Hepatitis B & C	Sorafenib n=79 (26%) Placebo n=80 (26%) NB other patients may have alcohol as aetiological feature combined with other aetiologies eg Hepatitis B & C	Histological Sorafenib 30% Placebo 31% Clinical Sorafenib 29% Placebo 28%	Sorafenib 140 vs 159 (46.8 vs 53.2%) Placebo 153 vs 150 (50.5 vs 49.5%)	Sorafenib 8.4 Placebo 11.9 Macroscopic vascular invasion Sorafenib 108 (36% Placebo 123 (41%)	Sorafenib 284/14/1 (95/5/0.3) Placebo 297/6/0 (98/2/0)

6.3.3 Patient numbers

Figure 2 SHARP study Patient numbers



6.3.4 Outcomes

The **primary endpoints** in SHARP were:

1. Overall survival (OS)
2. Time to symptomatic progression (TTSP)

The primary endpoints were assessed independently. If the analysis were positive for either endpoint, the efficacy of sorafenib in HCC was to be considered established.

Secondary endpoints were:

1. Time to progression (TTP)
2. Overall Disease Control Rate (DCR)
[redacted]

Tertiary endpoints were:

1. Overall response rate
[redacted]

Other endpoints included safety, population pharmacokinetics, [redacted] [Of the 'other' endpoints, only safety results are reported in this submission.]

Due to the difficulty in distinguishing whether clinical deterioration or death in patients with HCC is as a result of HCC progression or deterioration of liver function and complications of underlying cirrhosis, TTP (based only on radiologically-documented tumour progression) was included as a secondary endpoint rather than progression-free survival (PFS). [redacted]

Table 5: Endpoints and measures included in the SHARP study (3;28)

ENDPOINT	DEFINITION & TIMING OF ASSESSMENT / MEASURE
PRIMARY ENDPOINTS	
Overall Survival (OS)	Measured from the date of randomisation until the date of death due to any cause. For patients lost to follow-up at the time of analysis, time to death was censored at their last date of follow-up. After the last dose of study medication and the 'end of treatment' visit, patients were entered into a follow-up period during which information on survival status was collected.
Time to Symptomatic Progression (TTSP)	The time from randomisation to the first documented symptomatic progression. Symptomatic progression was defined as progression based on • patient-reported cancer symptoms (a decrease of at least 4 points from baseline score based on subject response to the **FHSI-8 questionnaire** (see appendix 7))(40;41) • deterioration to **ECOG PS 4** (see Appendix 4) or • death For patients who had not progressed symptomatically at the time of interim analysis, TTSP was censored at the date of their last FHSI-8 assessment. Baseline FHSI-8 scores calculated on questionnaire response at day 1 of cycle 1 (pre-dose). FHSI-8 was completed by the patient every 3 weeks and scored centrally after each visit. Patients entering the study extension crossover phase completed the FHSI-8 at the 2-week pre-treatment screen. The FHSI-8 score is the sum of responses to 8 items and ranges from 0 to 32, the higher the score the worse the patient's symptoms. The minimally important difference (MID) for the FHSI-8 has been established as a 2-point change from baseline. The most conservative estimate of the MID is a 4-point change from baseline. ECOG PS was assessed at 2-week pre-treatment screen, day 1 of each treatment cycle and at the 'end of treatment' visit. This was continued for any patients entering the study extension crossover phase.

SECONDARY ENDPOINTS	
Time to Progression (TTP)	Time from randomisation to radiologically documented disease progression. Radiological progression was determined by the RECIST criteria (see Appendix 6). MRI or CT scans of the chest, abdomen and pelvis were performed within 28 days of start of treatment, at the end of every 6 week treatment 'cycle' and at 'end of treatment' visit. A second set of scans were developed for independent review. Conventional CT and MRI were performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT was performed using a 5mm contiguous reconstruction algorithm. Patients without tumour progression at the time of analysis were censored at their last date of tumour evaluation. For cases of unscheduled tumour assessments, the actual date of the radiological procedure was used to calculate TTP.
Overall Disease Control Rate (DCR)	The proportion of patients with a best response rating of complete response (CR), partial response (PR), or stable disease (SD) according to RECIST (see Appendix 6) that was maintained at least 28 days from the first manifestation of that rating. Tumour response was measured within 28 days of start of treatment, at the end of every 6 week treatment 'cycle' and at 'end of treatment' visit.
Quality of Life : FACT-Hep response rate (see Appendix 8)(41;42)	The FACT-Hep was completed at baseline and at week 12, and at the 'end of treatment' visit for patients discontinued before week 12. The FACT-Hep response rate was based on the proportion of patients who achieved the 8-point Minimal Important Difference (MID) in baseline total score to FACT-Hep total score at week 12 (or end of treatment). The FACT-Hep response rate analysis was based on the sum of the scores from patient responses to 45 items in the questionnaire (see Appendix 8); FACT-Hep total score ranges from 0 to 180. Higher scores on all scales of the FACT-Hep reflect better quality of life or fewer symptoms.(42)
TERTIARY ENDPOINTS	
Overall Response (OR) Rate	The proportion of patients with the best tumour response (PR or CR) achieved during treatment or within 30 days after termination of active therapy. Response was assessed by MRI or CT scan as per RECIST criteria (see Appendix 6). MRI or CT scans of the chest, abdomen and pelvis were performed within 28 days of start of treatment, at the end of every 6 week treatment 'cycle' and at 'end of treatment' visit. A second set of scans were developed for independent review.
[redacted]	[redacted] Patients who had not progressed or died at the time of analysis were censored at the date of their last tumour assessment. See 'Overall Response' endpoint for method / frequency of response assessment.
[redacted]	[redacted] See 'Overall Response' endpoint for method / frequency of response assessment.
[redacted]	[redacted]

OTHER ENDPOINTS	
Safety	Study visits for evaluation of safety occurred every 3 weeks during the treatment period; safety was also evaluated during screening and at the end of treatment visit. Toxicities / adverse drug reaction including serious adverse events were recorded using the verbatim investigator term as well as the NCI-CTCAE*(39) Laboratory, haematology, biochemistry and PT/PT-INR/PTT measures were assessed within 2 weeks prior to treatment start, on day 1 of every treatment cycle and at the end of treatment visit. Vital signs:- blood pressure, heart rate, respiratory rate, temperature. ECG – measured within 28 days of treatment start and then at 'end of treatment' visit. Adverse event = *any untoward medical occurrence in a patient administered a pharmaceutical product that is temporally associated with the use of that product, regardless of whether it is considered related to the product.* Serious adverse event = *an adverse event that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, requires medical or surgical intervention to prevent any of these outcomes, or is determined by the investigator to be a medically important event.*

* National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events [CTCAE] version 3.0(39)
PT=prothrombin time; INR=international normalised ratio; PTT=partial thromboplastin time

6.3.5 Statistical analysis and definition of study groups

The primary population for efficacy analysis was the intent-to-treat (ITT) population, which was defined as all randomised patients. In the SHARP study, 602 patients were randomised. Of these patients, 524 were men and 79 were women, and the median age was 67 years. Two hundred and ninety nine patients were randomised to sorafenib and 303 to placebo. Five hundred and ninety nine patients (n=297 sorafenib and n=302 placebo) received at least one dose of study medication and were valid for the safety analysis. The 3 randomised patients who did not go on to receive treatment due to adverse event (n=1) and protocol violations (n=2) were not considered valid for the safety analysis.

The main analysis was measured by log rank test (see Table 6). In addition to the final analysis of OS and TTSP, two formal interim analyses of OS were planned during the study – the first planned at 170 deaths and the second interim analysis planned when approximately 300 deaths had been observed. An alpha spending function (O'Brien-Fleming-type error spending function) was used to ensure that the false positive rate (alpha) for OS was less than or equal to 0.02 (1-sided). No interim analysis was planned for TTSP, however it was to be analysed if the study was stopped at an interim analysis, hence TTSP was analysed using data cut-off 17th October 2006. The efficacy of sorafenib was to be considered established if either analyses based on the co-primary efficacy endpoints were positive.

The null hypotheses are:
H_0: The overall survival function of placebo is the same or better than that of Nexavar
H_A: The overall survival function of Nexavar is better than that of placebo

H_0: The TTSP function of placebo is the same or better than that of Nexavar
H_A: The TTSP function of Nexavar is better than that of placebo

The efficacy of sorafenib is considered established if either of the null hypotheses for Overall Survival or TTSP are rejected.

Table 6: Primary efficacy variables with primary and secondary statistical methods(3;28)

PRIMARY EFFICACY VARIABLE	PRIMARY STATISTICAL METHOD	SECONDARY STATISTICAL METHOD
Overall Survival (OS)	1-sided Log rank test (overall α = 0.02 stratified as per randomisation i.e. by region, ECOG PS and tumour burden).	Cox Regression Model Kaplan-Meier(KM) estimates and survival curves for each treatment group. The differences of KM estimates at some time points e.g. 6 months, 12 months, and corresponding 95% confidence intervals (CIs) were also calculated between the sorafenib and placebo groups. For each treatment group, FHSI-8 scores were summarised by visit for observed values and changes from baseline using descriptive statistics. Graphs of average score changes were generated to see if a time trend existed.
Time to Symptomatic Progression (TTSP)	1-sided Log rank test (overall α = 0.005 stratified as per randomisation i.e. by region, ECOG PS and tumour burden).	

Overall survival was the main endpoint when considering study design and sample size calculation. A clinically meaningful improvement is defined as 40% increase in median OS compared to placebo. Assuming one-sided alpha of 0.02 and a randomisation ration of 1:1 (placebo:sorafenib) a total of 424 events (deaths) were required to achieve a power of 90%. Assuming a 3% rate for patients lost to follow-up, at least 560 patients were required to be randomised for the study to be sufficiently powered.

Missing data For patients with no baseline tumour evaluation or those who had only baseline data and no post-baseline tumour evaluation, efficacy variables related to tumour evaluation such as TTP, overall response, time to response, duration of response, were coded as missing. If a subject's overall best response (CR,PR,SD and PD) assessment was missing, the subject was included in the denominator but not the numerator for the calculation of best response rate and DCR.

Subgroup analyses Descriptive statistics for all efficacy variables were provided for subgroups that included race, sex, age (<65 years, ≥65 years), region (North America, South America and Europe), ECOG PS (0 versus 1 and 2), and tumour burden (presence of either macroscopic vascular invasion and/or extrahepatic spread versus none). The study was not powered to assess differential patient responses to treatment by subgroup.

Statistical analysis – secondary, tertiary and other endpoints

Table 7: Primary and secondary statistical methods for secondary, tertiary and other endpoints

STUDY ENDPOINT	PRIMARY STATISTICAL METHOD	SECONDARY STATISTICAL METHOD
Time to Progression (TTP)	1-sided Log rank test (overall α = 0.025 stratified as per randomisation i.e. by region, ECOG PS and tumour burden) Kaplan-Meier(KM) estimates and plots presented for each treatment group. Based on independent radiological assessment (using data up to cut-off date for 1st interim analysis of OS, 12th May 2006 i.e. after approximately 227 radiological progression events had occurred) [NB This analysis was delayed to the end of study]	Based on investigator radiological assessment (using data up to cut-off date for 2nd interim analysis of OS, 17th October 2006) [redacted]

STUDY ENDPOINT	PRIMARY STATISTICAL METHOD	SECONDARY STATISTICAL METHOD
Disease Control Rates (DCR)	Cochran-Mantel-Haenszel (CMH) test with 2-sided α of 0.05 adjusted as per randomisation, by region, ECOG PS and tumour burden. Estimates of DCR and ORR and corresponding 95% CIs were calculated for each treatment group and the differences between treatment groups were also calculated.	
Overall Response Rate		
FACT-Hep response rate	Analysis of the proportion of patients attaining the 8-point MID using a logistical model fitting terms of treatment group, ECOG PS, region, tumour burden and baseline score as covariates to evaluate HRQOL responses were different between treatment arms. A 1-sided alpha level of 0.025 was used in the analysis.	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
Safety [The population for safety analysis comprised all patients who received at least 1 dose of study medication.]	Incidence summarised by treatment group and NCI-CTCAE version 3.0 worst grade.	

As of data cut-off of 17th October 2006, a total of 468 patients had discontinued double-blind treatment: 242 (80.1%) placebo patients and 226 (76.1%) sorafenib patients (see Figure 2). Overall, 132 (n=61 placebo; n=71 sorafenib) patients were still receiving double-blind study treatment. After discontinuing study treatment, patients were to enter post-treatment follow-up. As of 17th October 2006, 36 (11.9%) placebo patients and 47 (15.7%) sorafenib patients were still in follow-up.

6.3.6 Critical appraisal of relevant RCTs

	SHARP study, Llovet 2008(3)
How was allocation concealed?	Bayer prepared computer-generated randomisation list. The randomisation number for each patient was provided through telephone interactive voice response system (IVRS). The unique randomisation number of each patient was used on all medication labels (placebo & active treatment). Placebo & active treatments were identical in appearance and given under identical conditions. Randomisation codes kept in individual sealed envelopes.
Randomisation Technique	Computer-generated randomisation list. Randomisation was done stratified by region, ECOG performance status (0 versus 1 or 2), and 'tumour burden (presence or absence of macroscopic vascular invasion (as determined through radiological assessment) and / or extrahepatic spread. The randomisation number for each patient was provided through telephone interactive voice response system (IVRS).
Was a justification of sample size provided?	Yes, see section 6.3.5 Power of study/sample size
Was follow-up adequate?	Yes. Period of recruitment: March 2005 to April 2006 During the follow-up period patients were assessed every 3 months until death for survival status and receipt of any new cancer treatment.
Were the individuals undertaking outcome assessment aware of allocation?	Independent assessors of response / progression were blinded to the treatment.
Parallel group or cross-over?	Parallel Group. At the second interim analysis, sorafenib was found to significantly prolong survival, which meant that all patients ongoing in the double-blind phase, as well as patients in follow-up were unblinded and given the opportunity to enter into an 'extension with crossover' study phase. After this point only safety data were collected.
Location effects	UK participants n=16 (3%)(n=7 placebo, n=9 sorafenib). Majority of subjects were noted as White (n=273 placebo; n=261 sorafenib). Eighty seven per cent of the placebo patients (n=263) were from 'Europe & Australasia' as were 88% (n=263) of the sorafenib patients. No location effect likely.
Dosage regimens	As per SPC (see Appendix 1) Sorafenib 400mg b.d. for as long as a clinical benefit is observed or until unacceptable toxicity occurs.
Were study groups comparable?	Yes, demographic, baseline and surgical characteristics were similar across treatment groups.
Were the statistical analyses used appropriate?	Yes
Was an intention-to-treat (ITT) analysis undertaken?	Intention-to Treat analysis used See section 6.3.2
Confounding factors?	None identified. The study design and selection and measurement of endpoints were discussed and agreed with the US and European licensing authorities prior to study initiation.

6.4 *Results of the relevant comparative RCTs*

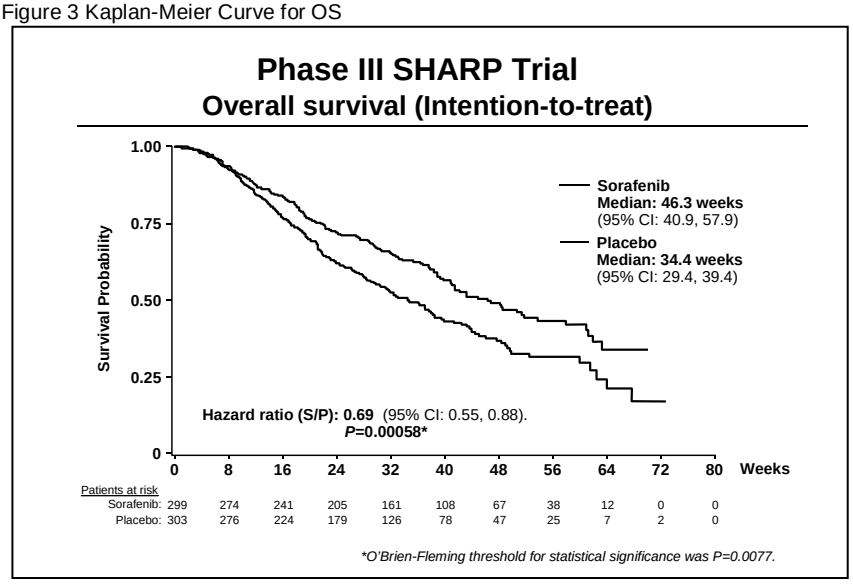
Primary endpoints – Overall Survival (OS), Time to Symptomatic Progression (TTSP)

The second interim analysis of efficacy data based on 321 survival events (178 events in the placebo arm, and 143 events in the sorafenib arm), demonstrated that sorafenib significantly prolonged overall survival compared with placebo. This led to early cessation of the trial.

Median overall survival was 34.4 weeks [95%CI 29.4, 39.4] in patients randomised to placebo and 46.3 weeks [95% CI 40.9, 57.9] in patients randomised to sorafenib (see figure 3). The stratified log-rank test had a 1-sided nominal p-value of 0.000583 and the estimated hazard ratio for survival (sorafenib over placebo) was 0.69 [95% CI 0.55, 0.87], representing a 30.7% reduction in hazard (risk of death) over placebo (or 44.3% increase in survival time over placebo) (*P* = 0.000583).

This represents a clinically meaningful and statistically significant improvement in overall survival attributable to sorafenib treatment, and also represents the first definitive demonstration of a meaningful survival benefit with any systemic treatment for HCC versus placebo.

Figure 3 Kaplan-Meier Curve for OS



The efficacy of sorafenib was also supported by the survival rates at 3, 6 and 12 months. The 3,6 and 12 month survival rates for sorafenib vs placebo are 86% vs 83%, 71% vs 61%, 44% vs 33% respectively (p=0.009).

TTSP, a co-primary outcome, was defined in the SHARP study as time from randomisation to the first documented symptomatic progression, based on patient-reported symptoms (PRO), deterioration to Eastern Cooperative Oncology Group (ECOG) performance status (PS) 4 or death.

The primary analysis of the TTSP demonstrated no statistically significant difference between the sorafenib and placebo arms. Median TTSP was 18 weeks [95%CI 15, 21] for sorafenib-treated patients and 21.1 weeks [95%CI 18.4, 27.4] for placebo. The hazard ratio was 1.08 (0.88, 1.31) for sorafenib over placebo which is not statistically significant (p=0.77). These results, inconsistent with sorafenib's positive impact on overall survival, suggest that the FHSI-8 questionnaire may have been too sensitive to offer reliable information about the impact of treatment on symptomatic tumour progression. The FHSI8 questionnaire is a patient-oriented outcome instrument that may have been influenced by both the toxicity of the drug, as well as the effect of tumour symptom response. The lack of significant differences in FHSI8-TSP might reflect the impact of early reporting of sorafenib toxicities on FHSI8 scores.

Secondary endpoints

Time to Progression (TTP)

Analyses of TTP based on both independent (primary analysis) and investigator assessments demonstrated a statistically significant improvement in patients treated with sorafenib compared with placebo.

By independent assessment, the median TTP was longer for the sorafenib arm 24 weeks [95% CI 18, 30]) than the placebo group 12.3 weeks (95% CI 117, 17.1). The hazard ratio for TTP was 0.58 (95% CI: 0.45, 0.74) representing a 42.4% reduction in risk of progression (or 73.5% improvement in TTP) in patients treated with sorafenib compared with placebo (P=0.000007)(3;28).

[redacted]

Table 8: Results of analyses of the TTP endpoint

	Independent Assessment (cut-off date 12th May 2006)		**Investigator assessment** (cut-off date 17th October 2006)		[redacted]	
	Sorafenib n=299	Placebo n=303	Sorafenib n=299	Placebo n=303	Sorafenib n=299	Placebo n=303
Number of progressions	107 (35.8%)	156 (51.5%)	181 (60.5%)	222 (73.3%)	[redacted]	[redacted]
Median TTP	24 weeks [95% CI 18, 30]	12.3 weeks [95% CI 11.7, 17.1]	17 weeks [95% CI 13,18]	11.9 weeks [95% CI 11.1, 12.4]	[redacted]	[redacted]
Hazard ratio (Sorafenib/placebo)	0.58 [95% CI 0.45,0.74] *p=0.000007*		0.6889 [95% CI 0.5634, 0.8423] *p=0.000130*		[redacted]	

Sensitivity analyses using scheduled radiological assessment dates rather than actual visit dates also concluded that sorafenib significantly prolongs TTP compared to placebo.

PFS was included in the SHARP study as a sensitivity analysis of TTP to evaluate the impact of deaths before progression. Based on independent tumour assessment and actual visit date, PFS rates at 4 months were 62% for sorafenib compared with 42% for placebo. These results support those reported for TTP.

Disease Control Rate (DCR)

In the SHARP study, DCR was higher in the sorafenib arm (43% [n=130]) than in the patients receiving placebo (32% [n=96]).

Tumour response

Table 9: Analyses of Tumour Response parameter per independent and investigator assessment

	Independent Assessment *(as of 12th May 2006)*		**Investigator assessment**	
	Sorafenib n=299 (%)	**Placebo n=303 (%)**	**Sorafenib n=299 (%)**	**Placebo n=303 (%)**
Number evaluated radiologically post-baseline	272	279	276	276
Best Response				
-complete response (CR)	0	0	0	0
-partial response (PR)	7 (2.34)	2 (0.66)	18 (6.02)	8 (2.64)
-stable disease (SD)	211 (70.57)	204 (67.33)	181 (60.54)	167 (55.12)
-progressive disease (PD)	54 (18.06)	73 (24.09)	77 (25.75)	101 (33.33)
-not assessable	27 (9.03)	24 (7.92)	23 (7.69)	27 (8.91)

	Independent Assessment *(as of 12th May 2006)*		Investigator assessment	
	Sorafenib n=299 (%)	**Placebo n=303 (%)**	**Sorafenib n=299 (%)**	**Placebo n=303 (%)**
Mean Time to Response	[redacted]			
Median duration of response				

No complete responses (CRs) were observed but there were 7 partial responses (PRs)(2%) in sorafenib-treated patients and 2 PRs (1%) in the placebo group. Stable disease was reported for 211 patients (71%) receiving sorafenib and 204 (67%) placebo-treated patients.

[redacted]

Health-related quality of life

Approximately 8% more placebo than sorafenib patients (19.6% versus 11.5%, respectively) achieved the 8-point MID for the FACT-Hep at Cycle 3, Day 1 or end of treatment visit.

[redacted]

Safety data are reported in Section 6.7 - Safety.

Subgroup analyses

Analysis of overall survival by subgroup, using the patient stratification variables at randomisation, showed a consistent significant trend favouring the sorafenib arm for nearly all subgroups. The subgroup analyses were intended to be descriptive only. The study was not powered to assess differential patient response to treatment in subgroups, and no adjustments were made for multiple comparisons.

An exploratory multivariate analysis with the use of a Cox proportional-hazards model identified eight baseline characteristics that were prognostic indicators for overall survival: ECOG performance status, presence or absence of macroscopic vascular invasion, extent of tumour burden (defined as presence or absence of vascular invasion, extrahepatic spread, or both), Child–Pugh status, and median baseline levels of alpha-fetoprotein, albumin, alkaline phosphatase, and total bilirubin. After adjustment for these prognostic factors, the effect of sorafenib on overall survival remained significant (hazard ratio, 0.73; 95% CI, 0.58 to 0.92; P = 0.004). A prespecified subgroup analysis showed a consistent survival benefit for sorafenib over placebo in most of the subgroups analysed:

Table 10: Subgroup analysis SHARP study

Subgroup	Median OS (months)		Hazard Ratio (95% CI)
	Sorafenib	Placebo	
ECOG PS(43)			
0	13.3	8.8	0.68 (0.50, 0.95)
1-2	8.9	5.6	0.71 (0.52, 0.96)
Macroscopic vascular invasion ***or*** extrahepatic spread or both(44)	8.9	6.7	0.77 (0.60, 0.99)
No tumour burden	14.5	10.2	0.52 (0.32, 0.85)
With macroscopic vascular invasion(28)	[redacted]	[redacted]	0.68 (0.49, 0.93)
No macroscopic vascular invasion	[redacted]	[redacted]	0.74 (0.54, 1.00)
No extrahepatic spread(28)	[redacted]	[redacted]	0.55 (0.39, 0.77)
Alcohol-related HCC(45)	10.32	7.99	0.76 (0.50, 1.16)
Baseline Transaminase levels(46)			
Normal ALT/AST (<1.8 x ULN)	13	9	NR
Mild ALT/AST (≥1.8 to ≤3 x ULN)	11	8	NR
Moderate ALT/AST (>3 x ULN)	8	5.5	NR
Hepatitis C(47)	14	7.9	0.58 (0.37, 0.91)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

NR=not reached

Compared with placebo, sorafenib prolonged OS in patients with advanced HCC irrespective of ECOG PS(43). Sorafenib also prolonged OS in patients with advanced HCC irrespective of presence or absence of macroscopic vascular invasion and/or extrahepatic spread(44). Treatment was well tolerated across all subgroups.

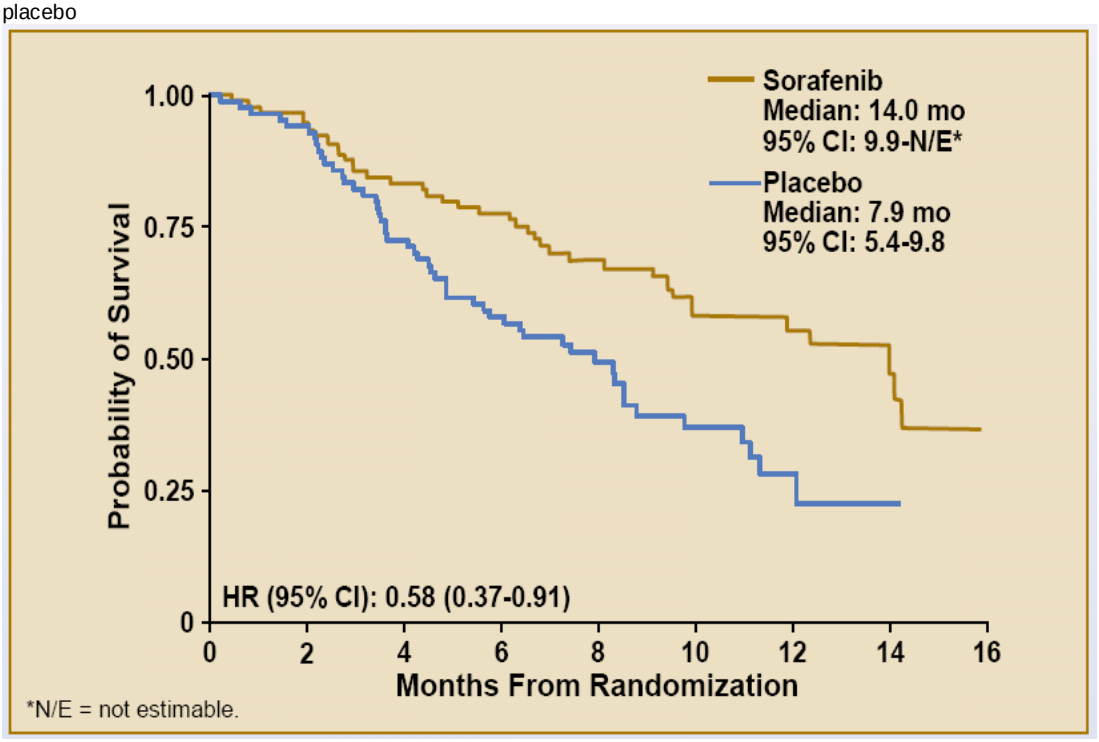
ECOG PS and “tumour burden” (defined as presence of macrovascular invasion and/or extrahepatic spread) contribute to the BCLC stage, which distinguishes between patients with different prognoses (from early to end-stage). [redacted]

Overall, these data suggest that sorafenib extends survival across established prognostic subgroups, and further support sorafenib as the new standard of care in this setting.

Similar clinical benefit was observed in patients with varying baseline transaminase levels. Hence, no dose reduction is recommended in HCC patients with mild or moderate elevated baseline ALT/AST(46).

The subgroup analysis in Hepatitis C virus (HCV) patients was presented at the 2008 ASCO Gastrointestinal Cancer Symposium(47). As in the overall SHARP trial population, treatment with sorafenib improved overall survival (Figure 4) over placebo (sorafenib 14.0 months, placebo 7.9 months) in HCV-positive patients.

Figure 4: Overall survival in patients with serological evidence of HCV infection following treatment with sorafenib or placebo



Supporting RCT data

Asia Pacific Study(23;36)

Results from the SHARP study are supported by the Asia-Pacific RCT, which showed superiority for sorafenib over placebo for overall survival (OS) and time to progression (TTP), thus demonstrating efficacy in a different population in patients with different leading aetiologies.

In the Asia Pacific study (study 11849), 226 patients from China, Korea and Taiwan with advanced HCC were randomised to receive either sorafenib (n=150) or placebo (n=76). The study was designed in parallel with the SHARP study and inclusion and exclusion criteria were similar.

Sorafenib significantly prolonged overall survival (OS), despite more advanced disease compared to patients enrolled in SHARP. The median OS was 18.2 weeks[1] in placebo patients compared to 28.2 weeks in sorafenib--treated patients. The hazard ratio for this improvement was 0.68 (P=0.014) representing a 47% increase in OS with sorafenib. The 6-month overall survival rate was 53.3% in the sorafenib group and 36.7% in the placebo group.

The absolute increase in median overall survival rates were smaller (although the HR differentials almost match) when compared to results from the SHARP trial. This is most likely explained by the fact the patients in the Asia-Pacific trial had a poorer status and more advanced tumour stage as exemplified by a higher rate in extrahepatic spread(48). This is in accordance with the SHARP data where patients with poorer status(43) and extra-hepatic spread and/or macroscopic vascular invasion(44) also showed lower survival rates, although the significant difference and benefit between sorafenib and placebo was maintained throughout the subgroups.

The Asian-Pacific study also measured TTSP using the Functional Assessment of Cancer Therapy - Hepatobiliary Symptom Index (FSHI8) questionnaire with similar results (15.2 vs 14.8 weeks)(23). Reasons for lack of differences between the arms are highlighted elsewhere.

Sorafenib significantly prolonged TTP in the Asia-Pacific study. Median TTP was 6.1 weeks in placebo patients and 12.2 weeks with sorafenib. The hazard ratio for this improvement was 0.57 (P=0.0005) representing a 76% improvement in TTP. Sorafenib was well-tolerated and had manageable side effects. The reduced benefit compared to the SHARP study, also seen with overall survival, can again be explained by patients in the Asian trial having poorer performance status and more advanced tumour stage.

DCR was 35% [95% CI 28,34] in the sorafenib arm and 16% [95% CI 8, 26] in the patients receiving placebo. Five of 150 patients in the sorafenib group (3.3%) achieved a partial response and 81 of 150 patients (54%) had stable disease. In the placebo group, one patient achieved a partial response (1.3%) and 21 patients had stable disease (27.6%).

In the preplanned subgroup analysis, sorafenib provided clinical benefit in all groups, despite some patients having characteristics associated with poor prognosis e.g. extrahepatic spread, macroscopic vascular invasion and HBV infection.

6.5 *Meta-analysis*

Not applicable. Evidence from only one RCT was fully available for analysis and relevant to the decision problem (SHARP study)(3). The Asia-Pacific trial(36) corroborates the findings from the SHARP study, however patients had different baseline and demographic characteristics making it inappropriate to perform a meta-analysis.

[1] A conversion factor of 4.34 was used to convert months to weeks

6.6 *Indirect/mixed treatment comparisons*

Not applicable.

6.7 *Safety*

Of the patients valid for safety analysis in the SHARP study, 284 (93.8%) of the placebo group and 227 (75.7%) of the sorafenib group received an average daily dose of at least 80% of the planned daily dose, and 269 (88.8%) of the placebo group and 204 (68.0%) of the sorafenib group received an average daily dose of at least 90% of the planned daily dose. The mean daily dose administered was 774.8 mg for placebo and 710.5 mg for sorafenib. The median duration of treatment up to the cutoff date for data collection (17 Oct 2006), was 18.6 weeks in the placebo group and 23 weeks in the sorafenib group(28).

There are no studies directly comparing sorafenib, as a single agent, with alternative active treatments in advanced HCC.

Data on the safety of sorafenib in advanced HCC relevant to the UK is drawn mainly from the SHARP study, an international multicentre phase III double-blind, placebo-controlled RCT(3;28). The study design, patient characteristics, statistical analysis, and clinical results are described fully earlier in section 6. In the SHARP study, the population for safety analysis comprised all patients who received at least one dose of study medication (n=599; placebo n=302 and sorafenib 400mg bd n=297). Supporting data on the safety of sorafenib in advanced HCC comes from 137 patients in a phase II uncontrolled study(24).

In both studies patients were monitored for adverse events using the NCI-CTC, although the SHARP RCT used Version 3.0(39) and the phase II study used version 2.0(49). There were many significant modifications between NCI-CTC v2.0 and NCI-CTC v3.0, including an increase from 295 adverse events to well over 1000 terms, and the addition of a 'Death' category. The results from both studies are therefore not directly comparable, however the data can be used to examine trends in adverse events.

The overall incidence of treatment-related adverse events was 80% in the sorafenib group and 52% in the placebo group, of which most were grade 1 or 2 (see Table 11). Serious adverse events were reported in 164 (54%) of placebo patients and in 153 (52%) sorafenib patients.

Table 11: Incidence of treatment-related adverse events reported for at least 5% of patients in either treatment arm in the SHARP study(3;28)

Adverse Event **NCI-CTCAE version 3.0 Category / Term**	**CTC GRADE**	**Placebo (n=302) n(%)**	**Sorafenib (n=297) n(%)**	**Phase II study(24)* (n=137) n(%)**
Any Event	ALL	158 (52%)	236 (80%)	NR
Cardiac General Hypertension	 3 ALL	 2 (1%) 6 (2 %)	 5 (2%) 15 (5%)	 NR
Constitutional Symptoms Fatigue	 3 4 ALL	 10 (3%) 1 (<1%) 47 (16%)	 9 (3%) 2 (1%) 64 (22%)	 13 (9.5%) 0 (0%) 41 (29.9%)
Weight Loss	 3 ALL	 0 (0%) 2 (1%)	 5 (2%) 28 (9%)	 NR
Gastrointestinal Anorexia	 3 ALL	 2 (1%) 10 (3%)	 1 (<1%) 41 (14%)	 2 (1.5%) 19 (13.9%)
Diarrhoea	3 ALL	5 (2%) 34 (11%)	25 (8%) 116 (39%)	11 (8%) 59 (43.1%)
Nausea	3 ALL	3 (1.0%) 23 (8%)	1 (<1%) 33 (11%)	0 (0%) 22 (16.1%)

Adverse Event NCI-CTCAE version 3.0 Category / Term	CTC GRADE	Placebo (n=302) n(%)	Sorafenib (n=297) n(%)	Phase II study(24)* (n=137) n(%)
Vomiting	3 ALL	2 (1%) 8 (3%)	3 (1%) 15 (5%)	0 (0%) 14 (10.2%)
Stomatitis	3 ALL	NR	NR	1 (0.7%) 15 (10.9%)
Pain Pain, Abdomen NOS	3 ALL	2 (1%) 9 (3%)	6 (2%) 24 (8%)	NR
Pulmonary / Upper Respiratory Voice Changes	ALL	2 (1%)	17 (6%)	NR
Dermatology / Skin Alopecia	ALL	5 (2%)	41 (14%)	14 (10.2%)
Dry Skin	ALL	12 (4%)	24 (8%)	NR
Hand-Foot Skin Reaction	3 ALL	1 (<1%) 8 (3%)	23 (8%) 63 (21%)	7 (5.1%) 42 (30.7%)
Dermatology – other (specify)	3 ALL	0 (0%) 2 (1%)	3 (1%) 16 (5%)	NR
Pruritus	3 ALL	1 (<1%) 22 (7%)	0 (0%) 25 (8%)	NR
Rash / Desquamation	3 ALL	0 (0%) 34 (11%)	3 (1%) 47 (16%)	1 (0.7%) 23 (16.8%)

*Publication only reports on grade 3 and 4 drug-related adverse events in ≥10% of all 137 patients
NR=not reported

The most common drug-related adverse events reported with sorafenib in both studies were dermatologic, constitutional and gastrointestinal, in particular, hand-foot skin reaction, alopecia, rash, fatigue and diarrhoea. and were predominantly grade 1 or 2 in severity (see Table 11). Diarrhoea (39% vs 11%), weight loss (9% vs 1%), hand–foot skin reaction (21% vs 3%), alopecia (14% vs 2%), anorexia (14% vs 3%) and voice changes (6% vs 1%) occurred at a significantly higher frequency in the sorafenib group than in the placebo group ($p<0.001$). These events were not unexpected based on the current knowledge of the safety profile of sorafenib. Although frequent, hand-foot skin reaction was the reason for permanent discontinuation of study drug in only 4 (1.3%) patients treated with sorafenib and in 1 (0.3%) placebo patients. It resulted in dose reductions in 5% patients treated with sorafenib, and was reported as a serious adverse event in only 2 patients, both in the sorafenib group.

Grade 3 drug-related adverse events included diarrhoea (8% in the sorafenib group vs. 2% in the placebo group, $p<0.001$), hand–foot skin reaction (8% vs. <1%, $p<0.001$), hypertension (2% vs. <1%, $p = 0.28$), and abdominal pain (2% vs. 1%, $P = 0.17$); there were no grade 4 drug-related adverse events in any of these categories in either study group. Grade 3 or 4 laboratory abnormalities occurred at similar frequencies in the two study groups, with the exception of grade 3 hypophosphatemia (11% in the sorafenib group vs. 2% in the placebo group, $P<0.001$) and grade 3 or 4 thrombocytopenia (4% in the sorafenib group vs. <1% in the placebo group, $p = 0.006$).

Hepatobiliary and haemorrhage events are of special relevance in HCC as frequent complications of the underlying disease. Analysis of hepatobiliary and bleeding events, showed that treatment with sorafenib does not result in an increased risk for the occurrence of these type of events. The incidences of serious hepatobiliary adverse events had a similar overall frequency in both treatment groups: 11% sorafenib patients and 9% placebo patients respectively. Within this category, liver dysfunction was reported in 7% patients treated with sorafenib and in 5% patients treated with placebo.

Serious haemorrhagic events and variceal bleeding were reported in 9% and 2% of sorafenib patients and 13% and 4% of placebo patients respectively. Haemorrhage events assessed as related to study drug, occurred in 11 (3.6%) placebo patients and 21 (7.1%) sorafenib patients. The majority of these events in the sorafenib group were Grade 1 or 2: 17 (5.7%) patients. Of the 7 sorafenib patients with bleeding events with an outcome of death, 2 (0.7%) were assessed as related to study drug(28).

The sorafenib SmPC (see Appendix 1) states that in multiple clinical trials haemorrhage (including. gastrointestinal, respiratory tract and cerebral haemorrhage) was reported commonly >1/10 patients and these adverse reactions may have a life-threatening or fatal outcome. The SmPC further states under Warnings & Precautions for use that an increased risk of bleeding may occur following sorafenib administration. If any bleeding event necessitates medical intervention it is recommended that permanent discontinuation of sorafenib should be considered.

Hypertension was reported more frequently in the sorafenib group than in the placebo group, the majority of events being grade 1 or 2. Drug-related hypertension was reported in 6 (2.0%) placebo patients and 15 (5.1%) sorafenib patients. The observation that sorafenib is associated with hypertension is consistent with experience in sorafenib treatment of renal cell carcinoma (RCC)(50), where the incidence of hypertension was 12% vs. 1% in sorafenib-treated and placebo-treated RCC patients respectively. Hence the continued recommendation on the Nexavar Summary of Product Characteristics (SmPC) (see Appendix 1) for blood pressure to be monitored regularly.

Renal failure (<1% and 3%), and cardiac ischaemia or infarction (3% and 1%) were similar in frequency as a serious adverse event. The most common serious adverse events of any cause (aside from death) were liver dysfunction (7% and 5%, respectively), diarrhoea (5% and 2%), and ascites (5% and 4%).

In the SHARP study, hypophosphataemia was reported in 34.9% sorafenib-treated patients compared with 11.2% placebo patients. It did not result in dose reductions or permanent discontinuations of study drug. This phenomenon has been reported in previous clinical studies involving sorafenib and its aetiology is as yet unknown(50). Increased lipase, previously described with the use of sorafenib in RCC, was seen with a similar frequency (grade 3/4) in placebo and sorafenib groups in the SHARP RCT.

The rate of discontinuation of the study drug due to adverse events was similar in the two study groups (38% vs. 37%). The most frequent adverse events leading to discontinuation of sorafenib treatment were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%). Dose reductions due to adverse events occurred in 26% of the patients in the sorafenib group and 7% of those in the placebo group, whereas dose interruptions due to adverse events occurred in 44% and 30% of the patients, respectively. The most frequent adverse events leading to dose reductions in the sorafenib group were diarrhoea (8%), hand– foot skin reaction (5%), and rash or desquamation (3%). Drug-related adverse events leading to permanent treatment discontinuation occurred in 34 patients in the sorafenib group (11%) and 15 patients in the placebo group (5%).

There were 13 deaths in the sorafenib group and 29 deaths in the placebo group that were not attributed to disease progression(3). Deaths assessed as related to study drug were reported in 6 (2.0%) placebo patients and 4 (1.3%) sorafenib patients. The 4 deaths in the sorafenib group assessed as related to study drug, were bleeding oesophageal varices (1), haemorrhage into the abdominal cavity (1), visceral arterial ischaemia (1), and renal failure (1). Renal failure was developed from pre-renal origin, following dehydration which was judged a drug-related event(51).

Study results from the Asia-Pacific sorafenib RCT support findings from the SHARP and phase II study(23;36). Sorafenib was generally well tolerated, with events predominantly being grade 1 or 2. The most common treatment-related adverse events were hand-foot skin reaction (45% vs 2.7%), diarrhoea (25.5% vs 5.3%), alopecia (24.8% vs 1.3%), fatigue (20.1% vs 8%), rash or desquamation (20.1% vs 6.7%) and hypertension (18.8% vs 1.3%).

It can be concluded from safety analyses of the SHARP study and the phase II and Asia-Pacific studies that sorafenib has a manageable toxicity profile in hepatocellular carcinoma patients where drug-related adverse events are recognisable and acceptable. The range and frequency of adverse events reported in the HCC studies is a fair representation of the safety profile already observed in previous clinical studies of sorafenib in renal cell carcinoma (RCC)(50) for which Nexavar has been licenced and marketed (in RCC) since late 2005 (US) / mid-2006 (Europe). Across both indications, the most commonly reported adverse events are hand-foot skin reaction and diarrhoea. This contrasts with doxorubicin or doxorubicin-containing combinations, the most typical systemic treatment alternative in the UK for this patient group other than best supportive care(19). RCTs involving doxorubicin-containing regimens demonstrate that doxorubicin is associated with significant myelosuppression (neutropenia, thrombocytopenia and anaemia)(52-54). It is also associated with gastrointestinal adverse events such as diarrhoea, stomatitis, nausea, vomiting and abdominal pain. Cardiotoxicity is also a well recognised complication of doxorubicin(55;56).

Please refer to the Nexavar SmPC (Appendix 1) for further details on the safety profile of sorafenib.

6.8 *Non-RCT evidence*

6.8.1 Details of how the relevant non-RCTs have been identified and selected

The systematic review, as described in section 6.1, identified one phase II study (Abou-Alfa, 2006) on the use of sorafenib in patients with advanced hepatocellular carcinoma (HCC)(24).

6.8.2 Summary of methodology of relevant non-RCTs

Trial Design(24;57)
Abou-Alfa 2006 reported on an international, multicentre, uncontrolled phase II study designed to evaluate the efficacy, toxicity, and pharmacokinetics of sorafenib in advanced HCC. The study enrolled 147 patients from 23 centres across 5 countries. Of these, 137 patients were subsequently treated as ten patients did not meet the inclusion / exclusion criteria. The study consisted of 3 phases: a 28-day screening phase, an active treatment phase, and a follow-up phase for survival data (until patient's death). After study completion, patients for whom it was determined to be medically appropriate, continued treatment with the study drug.

Study visits took place at 2-week intervals during the screening phase and 4-week intervals during the treatment phase. During follow-up, patients were telephoned at 3-month intervals. The study used a 3-stage design, recruiting a total of 26 patients by the first stage, 71 by the second and 135 by the third stage with 2 planned interim analyses after the availability of at least three-months data on tumour response for stages 1 and 2. The larger than planned accrual is accounted for the fact that accrual was not halted during interim analyses and continued during the 3-month maturation of response data.

Population under study (Inclusion & Exclusion criteria)
Patients with measurable, histologically proven, inoperable HCC who had not received prior systemic treatments for HCC were eligible for enrollment. Inclusion criteria included Eastern Cooperative Oncology Group performance status of 0 or 1; Child-Pugh (CP) score of A or B; life expectancy of at least 12 weeks; elevated alphafetoprotein (AFP) level and adequate haematologic, hepatic, and renal function. HBV or HCV infection status at baseline was collected from medical history or laboratory tests. Patients with tumors of mixed histology or fibrolamellar variant, pregnant or lactating women, or those requiring systemic anticancer therapy, biologic-response modifiers, or CYP34A inhibitors or with medical/psychological/social problems that might affect study participation or evaluations were excluded.

Study interventions
400mg of sorafenib twice daily orally on a continuous daily basis until disease progression, death or withdrawal from the study for other reasons. Dose reductions were permitted to predefined levels of 200mg twice daily and subsequently to 200mg once daily for adverse events related to study interventions.

Treatment compliance(57)
The number of tablets dispensed to and returned by each patient was recorded. Of the 125 patients who had discontinued study treatment at the time of analysis and internal report completion, the median number of cycles (28 days treatment) delivered was 4 (range 1 to 17) and 74% patients received 6 or fewer cycles. The mean average daily dose was 708.4mg (Standard deviation 153mg). Of the 137 subjects who took at least one dose of study drug, 81 subjects had a dose change or interruption. This included: 37 patients (27%) had dose reductions and of these 31 (23%) had dose reductions due to drug-related adverse events.

Concomitant medications(57)
The following treatments were permitted:

- Prophylactic use of G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF) or erythropoietin, provided they were not substituted for a required dose reduction and no dose adjustment was made within 2 months prior to or during the study
- Palliative and supportive care for any underlying illness was permitted. Subjects could receive bisphosphonates while on study drug. Palliative radiotherapy during the study was allowed provided that in the opinion of the investigator, the subject did not have PD, no more than 10% of the subject's bone marrow was irradiated, and the radiation field did not encompass a target lesion
- Prior local therapy such as surgery, hepatic arterial embolisation, chemo-embolisation therapy, radiation therapy, radiofrequency ablation, or cryo-ablation (as per inclusion criteria). Local therapy applied to both target and non-target lesions must have been completed at least 8 weeks prior to study inclusion.
- Concurrent treatment with octreotide was not permitted except for acute management of bleeding oesophageal varices.

The following treatments and medications were not permitted:

- Any systemic anticancer treatment or any agent administered with antineoplastic intent, including chemotherapy, immunotherapy, vaccines or hormonal therapy given before study entry or during study treatment. Anticancer therapy was defined as any agent or combination of agents with clinically proven anticancer activity administered systemically, with the purpose of affecting the cancer, either directly or indirectly, including palliative and therapeutic endpoints. In certain cases, local anticancer therapy (as per inclusion criteria) was allowed.
- Other investigational therapy
- Use of ketoconazole, itraconazole, ritonavir, and grapefruit juice
- Use of raf kinase inhibitors, MEK, or farnesyl transferase inhibitors, Use of biologic response modifiers such as G-CSF, within 3 weeks of study entry. Granulocyte colony-stimulating factor and other haematopoietic growth factors could be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated, or at the discretion of the investigator; however, they could not be substituted for a required dose reduction. Chronic erythropoietin treatment prior to the study entry or during the study was permitted.
- Treatment with non-conventional therapies (such as herbs) was not permitted although vitamins and mineral supplements were permitted.

Outcomes, assessments and definitions(28;57)
The primary endpoint in the phase II study was objective tumour response rate. Tumour response was assessed according to modified WHO criteria(58) (see Appendix 9) with investigator-assessed bidimensional tumour measurements performed at baseline and every 8 weeks. Independent radiologic assessment was also performed for patients with baseline and at least one post baseline imaging measurement. Stable disease was required to last at least 16 weeks.

Secondary endpoints were:

1. Duration of response – calculated from date of first administration of sorafenib until documented PD in subjects who had an objective response.
2. Time to response – calculated from date of first sorafenib administration to the date of CR or PR confirmation
3. TTP – calculated from date of first administration until first documented PD
4. PFS – calculated from the first date of receiving sorafenib until first documented PD or death (if death was earlier than PD)
5. Duration of stable disease & Proportion of patients with stable disease – calculated from date of first administration of sorafenib until a documented PD or response.
6. Overall Survival – calculated from date of first sorafenib administration until death.
7. Safety – Toxicities / adverse drug reactions summarised by NCI CTC version 2.0 criteria(49). Medical history, physical examination and vital signs. Assessed day 1, day 15 of cycle one, day 1 of each subsequent cycle and at final visit (30 days after last drug administration).

Statistical analysis and definition of study groups

The primary population for efficacy analysis was the intent-to-treat (ITT) population, which was defined as those receiving at least one dose of sorafenib and that had post-treatment data available. All results are thus based on 137 patients. The 10 enrolled patients who did not go on to receive treatment did not meet inclusion / exclusion criteria.

Statistical analysis – primary outcomes

The study used a 3-stage design, designed to recruit a cumulative total of 26 patients for the first stage, 71 for the second and 135 for the third stage with 2 planned interim analyses after the availability of at least three-months data on tumour response for stages 1 and 2.

The null hypothesis is:
H_0: The response rate for sorafenib is 7% or less

And the alternative hypothesis is:
H_A: The response rate for sorafenib is $\geq$ 15%

Under the null hypothesis, sorafenib was rejected as a cytoreductive agent if the response rate was $\leq$ 7% and accepted if response was at least 15%. Using a one-sided alpha of 0.05 (probability of accepting the regimen if true response $\leq$ 7%) and a beta of 0.100 (probability of rejecting the regimen if the true response rate $\geq$ 15%), the study progressed using the 3-stage design. The first interim analysis considered a) one confirmed CR / PR b) two confirmed minor responses (MRs) c) two $\geq$ 50% reduction in AFP d) three patients confirmed with either MRs or $\geq$ 50% reduction in AFP or SD for 12 weeks. If none of these were met the null hypothesis was accepted. If a) was met, stage two could proceed. If a) was not met but at least one of the other three conditions was met, stage 2 could proceed due to potential clinical benefit of sorafenib. In the second interim analysis the null hypothesis was accepted if 5 or fewer patients had a CR or PR. The null hypothesis was rejected if at least 11 patients had confirmed CR or PR. If 6-10 patients responded accrual proceeded to stage 3.

Best response rates, stable disease or PD rates were calculated with 95% CIs. TTP, time to response, duration of response and overall survival were summarised with Kaplan-Meier estimates.

At the time of analysis and internal report completion, 125 patients had discontinued from the study (see Table 12), the most common reason being for PD (74 patients (59%))(57). At the time of full publication, 132 patients had discontinued treatment which included 79 PD, 27 adverse events, and 11 deaths(24).

Table 12: Primary reason for discontinuation from sorafenib treatment in the Phase II study

	Sorafenib N=137 (100%)
Ongoing patients	12 (9%)
Total patients stopping study treatment	125 (91%)
Reason for discontinuing double-blind treatment	
Progressive disease (PD)	74 (59%)
Adverse event	26 (21%)
- drug related	15 (11%)
- not drug related	11 (9%)
Death	10 (8%)
Consent withdrawn	8 (6%)
Non-compliant with study medication	5 (4%)
Lost to follow-up	2 (2%)

Baseline characteristics

The median age of patients enrolled and treated in study 10874 was 69 years (range 28-86). There were 84 patients (61%) over the age of 65. Patients were predominantly male (71%). Distribution between ECOG performance status 0 and 1 was exactly equal (n=68;n=69). Ninety-eight patients were Child-Pugh A, 38 Child-Pugh B status with data missing for 1 patient. Hepatitis B was confirmed in 23 patients (17%) and Hepatitis C in 66 patients (48%) with status missing in remaining patients.

6.8.3 Critical appraisal of relevant non-RCTs

The phase II study is an open, single arm, uncontrolled study. It is therefore not possible to directly compare results from this study with other RCTs.

Patients enrolled in the study came from the USA, Belgium, France, Italy and Israel. Patients from the UK would be expected to have similar baseline and demographic characteristics to the study population.

The dose of sorafenib utilised in this study is as described & indicated within the Nexavar Summary of Product Characteristics (see Appendix 1).

6.8.4 Results of the relevant non- RCTs

Independent assessment of responses identified no CRs, 3 PRs, 8 MRs and 46 patients with stabilisation of disease. Duration of the 3 PRs ranged from 12 to 14.5 months.

Table 13: Results of primary and secondary endpoints from the phase II uncontrolled study

Endpoint	**ITT analysis (n=137)**	
Response	**Independent assessment**:	**Investigator assessment:**
CR	0	0
PR	3 (2.2%)	8 (5.8%)
MR	8 (5.8%)	6 (4.4%)
SD	46 (33.6%)	50 (36.5%)
Median TTP	5.5 months	4.2 months
Median OS	Not evaluable	9.2 months

Time to response, PFS, and duration of stable disease were not reported in the publication but have been sourced from the study report. Of the subjects who had confirmed PR, time to response ranged from 49 days (approximately 1.6 months) to 296 days (approximately 9.9 months). Median time to response was 191 days. Median PFS (based on investigator assessment) was 123 days (95% CI: 108, 148). Median duration of stable disease was 126 days (95% CI: 112, 168). Results from the phase II study are consistent with those in the phase III study.

SUMMARY OF CLINICAL DATA (RCT & NON-RCT data)

- Patients with HCC present with advanced disease and limited treatment options mean patients typically have a very poor prognosis with 5 year survival rates of <5%. The phase III SHARP study demonstrates that sorafenib is the only systemic treatment to significantly prolong overall survival in advanced HCC, with a 44% improvement in survival compared to placebo (HR=0.69 [95%CI 0.55, 0.87], p=0.00058) (46.3 vs 34.4 weeks).

- The benefit of sorafenib over placebo is observed across established prognostic subgroups, supporting the broad applicability of the treatment in HCC patients. Sorafenib was effective and well tolerated regardless of ECOG Performance Status, degree of liver impairment and presence or absence of vascular invasion or extrahepatic spread, as well as in patients with aetiologies of hepatitis C virus (HCV) infection or alcohol abuse.

- The efficacy of sorafenib was further demonstrated by the survival rates at 3, 6 and 12 months and independent analysis of time to progression, where statistically significant and clinically meaningful improvement in favour of sorafenib was observed (median TTP 24 weeks for sorafenib patients, 12.3 weeks for placebo group; HR=0.58, p=0.000007).

- These data led to sorafenib being granted a licence for the treatment of HCC. In accordance with the evidence base outlined in the submission sorafenib is suitable for patients with advanced hepatocellular carcinoma who are unsuitable for or have progressed after surgical or loco regional therapies.

- A further randomised placebo-controlled phase III RCT, evaluating sorafenib in patients from the Asia-Pacific region, corroborates the results of the SHARP study. Sorafenib significantly prolonged overall survival compared to placebo (HR=0.68, p=0.014), representing a 47% increase in survival time. Median TTP was 12.2 weeks with sorafenib and 6.1 weeks with placebo (HR=0.57, p=0.0005).

- In addition, results from the phase II study (Abou-Alfa 2006), were consistent with those observed in the SHARP study (median overall survival 9 months [investigator-assessed], median TTP 5.5 months [independently assessed]).

- In the SHARP, Asia-Pacific and Phase II (Abou-Alfa 2006) studies, sorafenib was well tolerated, indicating that sorafenib has a manageable and acceptable safety profile.

6.9 Interpretation of clinical evidence

6.9.1

The decision problem addressed in the submission is the clinical benefit and cost-effectiveness of sorafenib as a treatment in those patients with advanced stage hepatocellular carcinoma (HCC) disease who have failed or are unsuitable for surgical or locoregional therapies.

Prior to the licensing of sorafenib in 2007, there were no standard effective treatment options for patients with advanced inoperable HCC. No systemic agent had shown survival benefit versus placebo in HCC in more than 75 randomised controlled trials(4) and, in most cases, such treatments were associated with a high rate of side effects. As a result, there are no treatments, other than sorafenib, with FDA and/or EMEA approval for advanced HCC.

Overall survival is an important outcome for HCC patients and is also the most easily defined and least subject to investigator bias(59). A treatment that can increase survival vs. best supportive care alone, would provide a significant advance and address an unmet need in this patient population. Sorafenib has been demonstrated to significantly prolong overall survival

compared with placebo / best supportive care by 44% and is the only treatment to have demonstrated a survival benefit in advanced HCC for over 30 years(3).

The SHARP and Asia-Pacific RCTs and the phase II study also assessed endpoints related to tumour response (or disease progression) e.g. TTP, PFS, DCR, response rate, using standard parameters for documenting response of solid tumours(60). In cancer patients, delay in disease progression, by means of tumour shrinkage or disease stabilisation, is likely to translate into clinical benefit and progression of disease is likely to translate in worsening of symptoms and increased risk of death.

The SHARP study demonstrates that sorafenib significantly extends overall survival time by 44% when compared with placebo in advanced HCC. During treatment, sorafenib patients achieved significant prolonged stabilisation of disease, as confirmed by the results for median TTP (24 weeks vs. 12.3 weeks) in comparison with placebo treatment(3). These results are supported by the Asia-Pacific RCT(23) and the phase II study(24) and prove clinically meaningful in a disease where current timescales from diagnosis to death are short, 'quality' of life poor, and use of NHS resources extensive due to complications of liver disease and the palliative nature of treatment.

The co-primary endpoint of TTSP in the SHARP study set out to measure any delay in the appearance or worsening of disease symptoms in the sorafenib-treated group from a patient perspective [by ECOG PS, FHSI-8]. There was no statistical difference between sorafenib and placebo for median TTSP (18 weeks vs. 21.1 weeks). This result is not in line with the above-reported survival, TTP and other benefits of sorafenib and it is possible that the FHSI-8 tool may have been inadequate to discern treatment-related side effects or effects of underlying liver cirrhosis from progression of HCC. Indeed, an expert panel convened by the American Association for the Study of Liver Diseases (AASLD) concluded that this endpoint is particularly hard to measure in cirrhotic patients with cancer, in whom the impairment of quality of life may be a consequence of the natural history of cirrhosis and not tumour progression(34) and suggested that 'Time to Symptomatic Progression' as an endpoint in HCC studies is not 'ready for clinical research at this point'.

How a patient experiences their disease and its symptoms can have a physical and psychological impact, and hence, affect their 'quality' of life - also measured in the SHARP study by means of the FACT-Hep questionnaire. Quality of life (QoL) analysis of FACT-Hep and its subscale responses indicates that while sorafenib patients maintain physical function, their overall quality of life did not seem to improve, however for the majority of patients QoL did not appear to worsen either. This is consistent with disease stabilisation as opposed to disease response.

At an advisory board, held in part to discuss issues surrounding the complexity of the disease and how this confounds the health economic and outcome data from a UK perspective, there was agreement that the underlying liver disease would have an important impact on quality of life, and that the FACT-G instrument used in the Phase III trial should not have been used to measure symptomatic progression and separate out the effect of the tumour and that of the liver disease on patients' health-related quality of life. The clinicians reported that the EORTC group had developed a HCC specific module of the EORTC instrument and that this should be used in future prospective studies. Furthermore, it was felt that due to the limited research to date in advanced HCC, additional research was necessary to be able to define relevant health states that could be used to get a societal valuation of quality of life, taking into account underlying liver disease and the impact of sorafenib.

Safety was an additional endpoint measured in both the SHARP and the phase II studies. This is clearly patient-relevant and the results verify the general tolerability and acceptability of sorafenib in advanced inoperable HCC.

In summary, the clinical data within this submission demonstrates sorafenib to be an effective systemic treatment for patients with inoperable advanced HCC, prolonging survival and delaying disease progression in patients for whom there is a lack of alternative therapy and a high unmet clinical need.

6.9.2

It is considered that results from the SHARP and phase II studies would be equally applicable to the patient population within routine clinical practice in England and Wales. The vast majority (87%) of participants in the SHARP study were European and Caucasian. The Asia-Pacific study results may be less applicable due to the difference in patient baseline and demographic characteristics, however, the positive results in a 'different' population demonstrate sorafenib's efficacy in a broad number of patients.

In all studies discussed, sorafenib was administered at the same dosage as that recommended in the Summary of Product Characteristics. It is an oral agent, convenient to administer, with a simple dosing regimen (400mg bd). This avoids the patient having to attend hospital for intravenous. No dose adjustment is needed for age, sex, bodyweight, mild, moderate or severe renal impairment or mild to moderate hepatic impairment.

The SHARP study recruited patients with good liver function (mainly Child-Pugh status A (95% vs. 98% sorafenib and placebo respectively) and reasonable performance status (ECOG 0-2). Patients in general clinical practice with advanced inoperable HCC will have mixed aetiology and varying degrees of severity of underlying disease, including poor liver function and performance status. There are limited data from this study in patients with Child-Pugh B liver impairment but there appears to be a meaningful treatment effect. Only one patient with Child-Pugh C at baseline was included in the SHARP study. [redacted]

Similar clinical benefit was observed in a subgroup analysis of varying baseline transaminase levels in patients from the SHARP study (46) and in the phase II study, sorafenib was equally well tolerated by Child-Pugh A and B patients (24). Hence, sorafenib is considered to be suitable for patients with Child-Pugh A or B status and no dose reduction is recommended in HCC patients with mild or moderate (Child-Pugh A and B) elevated baseline ALT/AST.

Since sorafenib is mainly eliminated via the hepatic route, exposure might be increased in patients with severe hepatic impairment. There are no data in patients requiring dialysis or patients with severe hepatic impairment.

Patients taking concomitant warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, international normalised ratio or clinical bleeding episodes and also monitoring of renal function should be considered in elderly patients. Blood pressure should be monitored regularly and treated as required in accordance with standard medical practice. In such advanced stage cancer patients, it is likely that these assessments would already take place routinely, regardless of whether they were being treated with sorafenib.

The higher acquisition costs of sorafenib versus 'best supportive care' needs to be considered relative to the clinical benefits and life extension and complications of other alternative approaches; this has been evaluated within the economic section of this submission. Consideration should also be given to the lack of alternative therapies in HCC leaving patients at this difficult 'end' stage in their life with few options and relief. On account of the small number of patients in this indication, sorafenib was granted European and US orphan drug status in April 2006.

7 Cost effectiveness

7.1 *Published cost-effectiveness evaluations*

7.1.1 Identification of studies

A literature search of economic evaluations of treatment of advanced unresectable hepatocellular carcinoma (HCC) was carried out.

The following databases were searched for identification of economic papers (to December 2008)

- Medline (Dialog Datastar)
- Embase (Dialog Datastar)
- The Cochrane Library Issue 4, 2008 (including NHS EED)
- Health Economic and Evaluations Database (HEED)

Nine studies were identified from the search and screening process(22). However, the search for relevant pharmacoeconomic literature revealed no studies of direct relevance to the sorafenib submission, with the exception of one abstract(61). This study demonstrated the cost-effectiveness associated with sorafenib compared to best supportive care. Using a Markov model, the model followed survival and time to progression (TTP) in monthly cycles based on extrapolation of patient level trial data over a patient's lifetime. Health effects were expressed as Life Years Gained (LYG) where LYG was longer for sorafenib compared to best supportive care (1.59±0.18 vs 1.06±0.10/patient). Detailed information was not available with which to populate / construct a UK-based model and the is based on costs/resources from the US third party payer perspective which are not likely to be the same as the UK.

No publications included relevant UK pharmacoeconomic analyses of sorafenib and therefore there is a requirement for a de-novo economic evaluation. The economic evaluations identified through this review can be used to inform the approach to this evaluation.

See Appendix 3, section 10.3.

7.1.2 Description of identified studies

N/A There were no relevant studies identified.

7.2 *De novo economic evaluation(s)*

7.2.1 Technology

7.2.1.1 *How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use*

Sorafenib is a multikinase inhibitor affecting tumor proliferation and angiogenesis, indicated for the treatment of hepatocellular carcinoma (HCC) (51). Consistent with the population from the pivotal phase III SHARP study, sorafenib is suitable for patients with advanced HCC who have not received prior systemic anti-cancer treatment for HCC. These are patients where surgical or locoregional therapies have failed or are unsuitable (These patients are referred to as advanced HCC hereafter).

The recommended dose of sorafenib in adults is 400 mg (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg) given continuously. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs (51).

In the pivotal trial on which the model is based, the dose of study drug was reduced in 96 (32.1%) subjects in the sorafenib group. The most frequent reason for dose reduction was adverse events (drug related or not), in 84 sorafenib subjects. Dosing was temporarily interrupted (at least once) in [redacted] sorafenib subjects. Adverse events were again the most frequent reason for dose interruptions in [redacted] sorafenib subjects. Overall, 227 (75.7%) of subjects in the sorafenib group and 284 (94%) in the placebo group received an average daily dose of at least 80% of the planned daily dose.

The efficacy data from the trials therefore reflects treatment interruptions and dosage reductions. In order to capture these effects the model uses a mean daily dose of 710.5 mg/day which takes into account the dose reductions and interruptions.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. In the pivotal trial the median duration of treatment was 23 weeks. This is consistent with a median time to progression of 24 weeks observed in the SHARP trial (28). The protocol allowed investigators to continue treatment beyond progression if clinical benefit was still observed. In the SHARP trial 23 (7.7%) patients continued treatment with sorafenib for a median of 129 days (28).

7.2.1.2 *Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators.*

No additional treatment continuation rule has been assumed.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

Sorafenib is indicated for the treatment of HCC. Consistent with the decision problem and the clinical trial evidence, the economic evaluation considers sorafenib in patients with advanced stage HCC, who have failed or are unsuitable for surgical or locoregional therapies.
The population included in the model is based directly on the pivotal SHARP trial (28). It is assumed that the advanced HCC population in England and Wales is similar to the population enrolled in this trial as discussed in section 6.9.2. Thus, the patient population is based on the inclusion criteria for the SHARP study:

- Histologically proven HCC
- Advanced HCC
- At least one measurable untreated lesion
- ECOG 0-2
- Child-Pugh class A
- No prior systemic treatment

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

The cost-effectiveness of selected subgroups was also examined. Subgroups from the clinical trial were selected according to the following criteria:

- had sufficient patient numbers in the SHARP trial (28) to allow for a valid analysis for overall survival (OS) and time to progression (TTP);
- had clinical relevance according to expert opinion.

The subgroup analysis assumes that:

- in the given subgroups the cost of each health state/treatment phase and adverse event is the same as for the overall population;
- the rate of adverse events, the probability of patients continuing on sorafenib after progression, and the length of this continuation is the same as for the overall population;
- the only difference compared to the overall population is TTP, OS and the average dose of sorafenib used.

Efficacy outcomes and doses using the patient level data from the SHARP trial (28) were estimated outside MS Excel using a statistical package (STATA®).

The following subgroups were evaluated as specified in the scope:

- According to age
    - Age =>65
- According to performance status
    - Child Pugh A
    - TNM I-III
    - Barcelona Clinic Liver Cancer (BCLC) Stage B
    - BCLC Stage C
- According to underlying cirrhosis or risk
    - Hepatitis C
    - No macroscopic vascular invasion
    - With macroscopic vascular invasion
    - No extrahepatic spread
    - No tumour burden (i.e., no macroscopic vascular invasion or no extrahepatic spread)

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

All obvious subgroups were considered.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients with advanced HCC, who have failed or are unsuitable for surgical or locoregional therapies, enter the model when they receive first-line treatment (sorafenib or BSC) until documentation of disease progression, but continue to be modelled until they finally exit the evaluation due to death. Patients may also exit the model as a result of death due to all cause mortality at any stage of the model.

7.2.3 Comparator technology

7.2.3.1 What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The economic model compares sorafenib against best supportive care (BSC) in patients with advanced HCC. In terms of the SHARP trial (28), BSC was defined according to the medical judgment of the investigator, but did not include surgery, radiation chemoemobolization, radiofrequency ablation, percutaneous ethanol injection, cryoblation, or other systemic treatments.

Less than 30% of patients are diagnosed in the early stages where liver tumours are more amenable to curative resection or transplantation. Some patients at later stages may be suitable for "loco-regional" treatments: ablation (radiofrequency ablation (RFA); percutaneous ethanol injection (PEI) or cryosurgery); (chemo) embolisation, and radiotherapy. For patients where surgical or loco-regional treatments have failed or are unsuitable, systemic therapy is the only active treatment option, although no treatment has ever been shown to improve overall survival in a randomised controlled trial. The prognosis for patients with advanced HCC is therefore bleak, with 5-year survival rates of <5%(18).

The uncertainty about best practice and treatment options for patients with advanced HCC is clearly highlighted by the lack of direction regarding specific therapy recommendations in guidelines produced prior to the introduction of sorafenib (see section 4.6).

UK guidelines for the diagnosis and treatment of HCC, commissioned by the British Society of Gastroenterology in 2003, do not specify a standard systemic therapy to be used in advanced HCC (5). The guidelines acknowledge the poor results obtained with current systemic anti-cancer agents, recommending the use of novel agents within the context of clinical trials. Research undertaken by Bayer on the treatments used by UK clinicians suggest limited active options aside from clinical trials of new agents and chemotherapy. Where chemotherapy was used, single agent doxorubicin or doxorubicin-containing combination therapies were more frequently mentioned, however these are only suitable for a minority of patients (19). With limited active options aside from clinical trials of new agents and chemotherapy (5), clinicians opt for best supportive care (BSC) as the most common patient management strategy. No other pharmacological treatments are approved by the FDA and/or EMEA for advanced HCC.

Conclusions from various reviews (6;7) meta-analyses (8) and systematic reviews (4;8-11) published over the past decade, conclude that no anti-cancer treatment has clearly been identified either as a 'gold standard', nor been shown demonstrably to improve overall survival vs. best supportive care (BSC). In such a situation it is justifiable, with new treatments, to compare active treatment with placebo or BSC alone as the control arm (7).

Doxorubicin is used in a minority of patients, but low overall response rates (10%–15%) and the risks associated with its use often outweigh any short-term benefits, and clinicians usually opt for a best supportive care (BSC) approach instead. A systematic review which identified studies involving sorafenib, doxorubicin, placebo or BSC in advanced HCC, confirmed this and informed on the heterogeneity in terms of dosage and treatment regimens, study population characteristics and outcome measures (22). The doxorubicin trials are generally small, with methodological flaws (e.g., lack of intention to treat analysis) and the heterogeneity of the patient groups makes the true effects of doxorubicin difficult to determine and compare. Hence data was insufficient to support even an indirect comparison with doxorubicin within the submission.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The analysis takes the perspective of the UK NHS. Quantification of personal and social services costs have been attempted however the evidence is limited and therefore these have been included as a sensitivity analysis. Only direct medical costs are included. Although advanced HCC has a significant impact on the family and carers of patients, the indirect costs and the quality of life effects of relatives or carers are not included.

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. What time horizon was used in the analysis, and what was the justification for this choice?

Patients with advanced HCC do not have a long life expectancy and a high proportion will die within the first year of diagnosis (62). However as some patients survive longer, in order to capture the full costs and outcomes of treatment, the model was run until less than 1 % of patients remained alive - 14 years. This time horizon should be sufficient to reflect all important cost and benefit differences between the treatments being compared. This is consistent with the scope for this appraisal. Analyses are presented for shorter time frames (i.e., 2 years, 5 years and 10 years) in the sensitivity analysis.

7.2.6 Framework

a) Model-based evaluations

7.2.6.1 Please provide the following.

- *A description of the model type.*

A cost-effectiveness analysis and cost-utility analysis are presented. Cost-utility analysis was chosen because this complies with the NICE reference case and cancer therapies have an impact on both morbidity (quality of life) and mortality (overall survival).

Advanced HCC is however a unique condition which poses methodological issues when evaluating the impact of new treatments on health related quality of life. Patients with hepatocellular carcinoma are heterogeneous, with a diverse range of underlying causes of cirrhosis, including hepatitis B, hepatitis C, alcoholism and haemochromatosis. In some patients, typically younger women, HCC may develop where cirrhosis is not present. Due to this diverse liver disease, it is particularly difficult to disentangle the effect of the advanced HCC, underlying liver disease and interventions on quality of life. More specifically, quality of life is likely to be affected by the symptoms of the underlying liver disease, including liver failure, irrespective of whether the tumour has stabilised or regressed. As a result, it is not possible to demonstrate the impact of treatments in advanced HCC on quality of life, and no robust and reliable utility data is available that separates out the effect of the primary liver cancer from the underlying liver disease causes. Taking this uniqueness of confounding comorbidities into consideration, the QALY may not be an appropriate outcome to measure the health benefit of patients with advanced HCC, therefore the cost per life years gained figures should also be given consideration.

Accounting for the progressive nature of HCC, a Markov approach represents an appropriate way of modelling a chronic disease when patients pass through a series of clearly defined and mutually exclusive health states.

The model encompasses outcome measures for costs, health outcomes and incremental cost-effectiveness. Outcomes for costs include those relating to drugs and medications, monitoring and adverse events, routine follow-up, hospitalisations, and palliative care. Health effects are expressed in terms of life years (LYs) and quality adjusted life years (QALYs). The analysis calculates incremental cost-effectiveness ratios (ICERs) as:

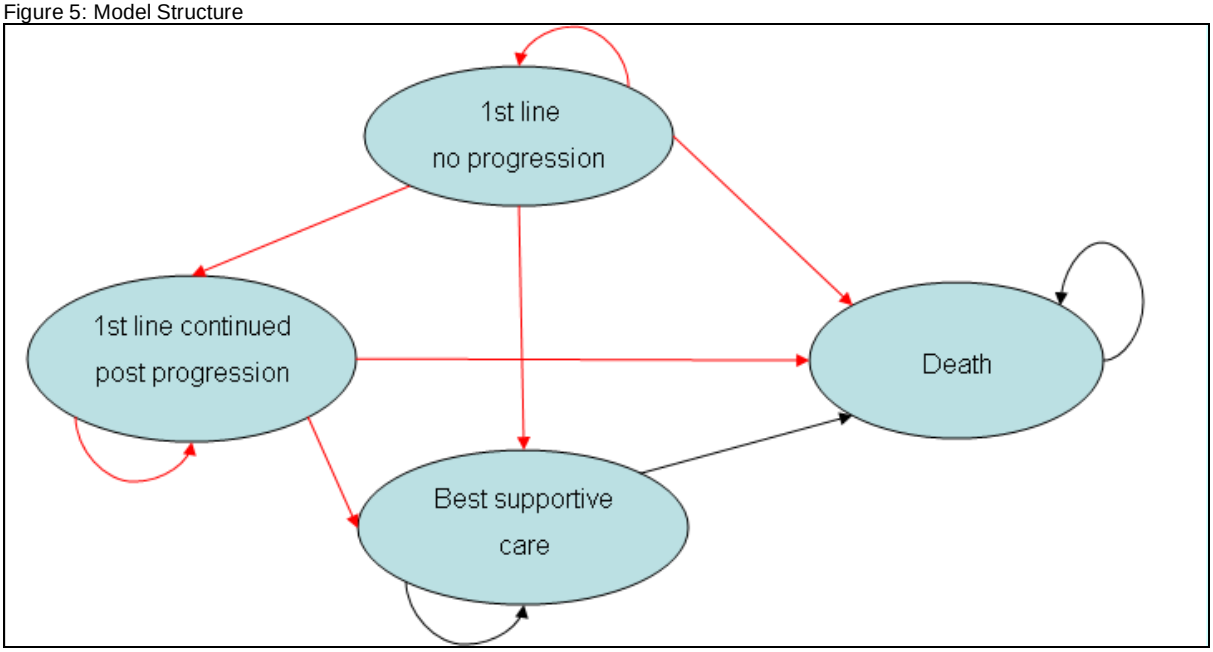
- Cost per LY gained; and
- Cost per QALY gained.

The outcomes measured in the SHARP trial (28) were time to progression and overall survival. Quality of life was also measured over time in the study using the descriptive Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) instrument. To derive utility scores an algorithm developed by Dobrez et al. (2007) (63) was used to map the HRQL measured by the FACT-G part of FACT-HEP instrument to time trade-off (TTO) utilities for selected health states in advanced HCC patients.

- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.

The model schematic is presented in Figure 5.

Figure 5: Model Structure



For transparency and interpretability, the model follows a simple structure. All patients start in the 1st line – no progression health state. Patients receive first-line treatment (with sorafenib or BSC) until documentation of further disease progression or until a treatment limiting adverse event (AE) occurs. At the point of progression, patients may either continue on first-line treatment (with sorafenib) or switch to BSC (palliative care). At any point in the model, patients may die due to all cause (general) mortality.

- *A list of all variables that includes their value, range (distribution) and source.*

Table 14: Efficacy Inputs (lognormal distribution parameters from the SHARP trial) (28)

	TTP		OS	
	Mu	**Sigma**	**Mu**	**Sigma**
Total population (base case)				
Sorafenib	4.822	0.983	5.791	1.147
BSC	4.513	0.804	5.465	1.019
Age =>65				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Child Pugh A				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
TNM Stage I-III				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
BCLC stage B				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
BCLC stage C				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis C from lab				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
With macrovascular invasion				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Without macrovascular invasion				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
No extra hepatic spread				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
No tumour burden				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]

Table 15: Utilities Input

			Distribution	Alpha	Beta	Source
Before progression						
Sorafenib	Mean	0.69	Beta	9.86	4.46	Bayer data on file 2007
	SD	0.12	Beta			
BSC	Mean	0.69	Beta	9.86	4.46	Bayer data on file 2007
	SD	0.12	Beta			
After progression						
Sorafenib	Mean	0.71	Beta	8.46	3.44	Bayer data on file 2007
	SD	0.13	Beta			
BSC	Mean	0.71	Beta	8.46	3.44	Bayer data on file 2007
	SD	0.13	Beta			
Disutility for AEs						
Sorafenib	Mean	-0.0087	Beta	11.22	-1300.47	Bayer data on file 2007
	SD	-0.0026	Beta			Calculation
BSC	Mean	-0.0087	Beta	11.22	-1300.47	Assumption
	SD	-0.0026	Beta			Assumption

Table 16: Adverse Events

	Mean	SD	Distribution	Alpha	Beta	Source
Rates						
Sorafenib	0.069	0.005	Beta	160	2174.67	SHARP trial
BSC	0.056	0.005	Beta	118	1972.23	SHARP trial
Weighted cost per cycle (£)						
Sorafenib	133.62	40.09	Gamma	11.11	12.03	Expert Opinion
BSC	220.77	66.23	Gamma	11.11	19.87	Expert Opinion

Table 17: Drug Costs Input (Sorafenib)

	Mean daily dose mg from SHARP	Mean cost per month (£)	Source
Total population (base case)	710.50	2,836	**Bayer Healthcare, Calculation (56)**
Age ≥65	[redacted]	[redacted]	
Child Pugh A	[redacted]	[redacted]	
TNM I-III	[redacted]	[redacted]	
BCLC stage B	[redacted]	[redacted]	
BCLC stage C	[redacted]	[redacted]	
Hepatitis C from lab	[redacted]	[redacted]	
Without macrovascular invasion	[redacted]	[redacted]	
With macrovascular invasion*	[redacted]	[redacted]	
No extrahepatic spread	[redacted]	[redacted]	
No tumour burden	[redacted]	[redacted]	

£2,980.47 for 112x200 mg tablets

* Data not available: assumed the daily dose to be the same as that for the total population

Table 18: Cost Inputs (£)

Type of costs	Mean	SD	Distribution	Alpha	Beta	Source
Active treatment – routine care						
Hospitalisation	65	19.43	Gamma	11.11	5.83	Expert Opinion
Medical staff visits	230	69.10	Gamma	11.11	20.73	Expert Opinion
Lab tests	124	37.24	Gamma	11.11	11.17	Expert Opinion
Radiological tests	61	18.22	Gamma	11.11	5.47	Expert Opinion
Total	480	-	-	-	-	-
Active treatment - after progression						
Hospitalisation	266	79.87	Gamma	11.11	23.96	Expert Opinion
Medical staff visits	480	143.88	Gamma	11.11	43.16	Expert Opinion
Lab tests	30	9.11	Gamma	11.11	2.73	Expert Opinion
Radiological tests	78	23.44	Gamma	11.11	7.03	Expert Opinion
Total	854	-	-	-	-	-

Type of costs	Mean	SD	Distribution	Alpha	Beta	Source
BSC - first line						
Hospitalisation	151	45.36	Gamma	11.11	13.61	Expert Opinion
Medical staff visits	225	67.61	Gamma	11.11	20.28	Expert Opinion
Lab tests	124	37.24	Gamma	11.11	11.17	Expert Opinion
Radiological tests	61	18.22	Gamma	11.11	5.47	Expert Opinion
Total	561	-	-	-	-	-
BSC – after progression						
Hospitalisation	386	115.77	Gamma	11.11	34.73	Expert Opinion
Medical staff visits	364	109.34	Gamma	11.11	32.80	Expert Opinion
Lab tests	30	9.11	Gamma	11.11	2.73	Expert Opinion
Radiological tests	78	23.44	Gamma	11.11	7.03	Expert Opinion
Total	859	-	-	-	-	-
At progression - one off cost						
Hospitalisation	0	0.00	Gamma	NA	NA	Expert Opinion
Medical staff visits	0	0.00	Gamma	NA	NA	Expert Opinion
Lab tests	104	31.34	Gamma	11.11	9.40	Expert Opinion
Radiological tests	134	40.09	Gamma	11.11	12.03	Expert Opinion
Total	238	-	-	-	-	-
End of life – one off cost	**0**	**0**	**Gamma**	**NA**	**NA**	

Unit costs and resource use inputs are provided in Appendix 13.

- *A separate list of all assumptions and a justification for each assumption.*

The economic evaluation analysis uses the following assumptions:

- The efficacy data from the multi-national trial (SHARP) is applicable to the proposed patient population in England and Wales and that the outcome differences observed in the trial translate to the population in the UK. SHARP was a multicentre trial with the UK as one of the participating countries. There is no reason to believe these patients would respond differently to treatment.
- The TTP and the OS observed in the treatment and the placebo group over 72 weeks can be extrapolated to the modeled time horizon, with the help of the lognormal distribution. Different distributions including Weibull, lognormal, Gompertz, loglogistic and exponential were fitted to the patient-level SHARP efficacy data and AIC (Akaike information criteria) was used as the measure of the goodness of fit. The distribution with the best fit (or the lowest AIC) was selected for the cost-effectiveness analysis, which was the lognormal distribution. Model predictions with the lognormal distribution were then compared to the results from the SHARP trial (28).
- The rate of future events is assumed to be independent of the events that occurred during previous cycles.
- BSC is the most frequently used therapy in HCC, i.e. the appropriate comparator to sorafenib; see section 4.4.
- After progression, 7.7% of patients are assumed to continue for a median of 129 days as observed in the SHARP trial (28).
- TTP was based on the trial investigators' assessment; (section 6.3). Although hybrid assessment was also available, investigator assessment was assumed the represent clinical practice in England and Wales.
- As the SHARP trial (28) did not report resource use or costs and no literature was found for costs for treating advanced HCC in the UK, these were collected separately outside the clinical trial using a resource use survey. We have assumed that resource use based on a UK physician survey is representative of clinical practice in the UK.
- Only those AEs occurring in at least 10% of the sorafenib patients have consequences from a cost or quality of life point of view.
- The rate of AEs is assumed to be constant over the time horizon. In clinical practice, AEs are likely to be experienced at different stages of treatment, particularly on initiation and then tachyphylaxis develops to the AE or they resolve following dose reduction. Hence, the assumption of uniformity is likely to overestimate the occurrence of AEs when treated with sorafenib.
- Disutilities due to AEs are not included after progression to avoid double counting, as most of these events are accounted for by the utility value of progression.
- The disutilities due to AEs can be estimated by subtracting the utility of a given health state with an AE from the utility of that health state without any AE.
- The extra costs incurred after progression in patients continuing on sorafenib in spite of progression, occur in the first year (do not need to be discounted). Hence, our conservative assumption tends to overestimate the effect of costs incurred after progression on the overall findings.

7.2.6.2 Why was this particular type of model used?

Accounting for the progressive nature of HCC, a Markov approach represents an appropriate way of modelling a chronic disease when patients pass through a series of clearly defined and mutually exclusive health states. The model is designed to track the progress of patients with advanced HCC as managed with sorafenib or BSC through a series of health states. The four health states in the model include: 1) first-line treatment – no progression, 2) first-line treatment

continued – post progression, 3) BSC - post progression, and 4) death. The states in the model are mutually exclusive as the patient can experience only one state at one point in time.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The model structure is consistent with clinical practice and, together with the assumptions, was validated by clinical experts. It is also in line with other economic models developed in oncology, with the main health states of alive without cancer/progression, alive with cancer/progression and dead (64-67). Disease progression and type of treatment are tracked throughout the model.

The model used monthly cycles to match treatment patterns and the continuous nature of the administration of sorafenib, i.e. patients' have the possibility to change from one health state to another every month.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The SHARP trial (28) and routine clinical practice in patients with advanced HCC were the key sources of information used to develop and inform the structure of the model. Furthermore the model structure is consistent with other economic models developed in oncology with the main health states of alive without cancer/progression, alive with cancer/progression and dead (64-67).

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The events that a patient with advanced HCC might experience include disease progression, adverse events (AEs) and death. The model conceptualises the disease by its clinical milestones such as disease progression and death following progression, which are the most important outcomes in the SHARP trial (28). These are tracked according to the type of treatment throughout the model. The model also tracks patients on active treatment (sorafenib) following disease progression, as the trial protocol allowed investigators to continue treatment if clinical benefit was still observed. At any point in the model, patients may die due to all cause (general) mortality.

In addition to the four health states included in the model, two health states were considered potentially suitable, but were ultimately excluded to avoid excessive and unnecessary technical complexity. These included 'adverse events' and 'end of life care'. Costs and disutilities associated with adverse events were included in the analysis regardless of the health state. The 'end of life care' was excluded as a separate state given that every patient – regardless of the comparator – had to pass through this state and there was no differentiation by prior treatment.

Disease progression is measured in the model by time to progression (TTP); however an analysis according to time to symptomatic progression is also presented in the sensitivity analysis. Time to symptomatic progression (TTSP) was defined as the time from randomization to the first documented symptomatic progression. Symptomatic progression was defined as a decrease of at least 4 points from baseline score based on patient responses to the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8) questionnaire, confirmed at the following 3 week scheduled assessment. All deaths were considered as symptomatic progression. Deterioration to an ECOG 4 status was also considered as symptomatic progression. The results for TTSP are not in line with the reported survival, TTP and other benefits of sorafenib and it is possible that the FHSI-8 tool may have been inadequate to discern treatment-related side effects or effects of underlying liver cirrhosis from progression of HCC. Indeed, an expert panel convened by the American Association for the Study of Liver Diseases (AASLD) concluded that this endpoint is

particularly hard to measure in cirrhotic patients with cancer, in whom the impairment of quality of life may be a consequence of the natural history of cirrhosis and not tumour progression (34) and suggested that 'Time to Symptomatic Progression' as an endpoint in HCC studies is not 'ready for clinical research at this point'. For further details see section 6.9.1.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The model has monthly cycles to match the treatment patterns and the continuous nature of the administration of sorafenib.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction is included in the model.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

The efficacy and the non-cost inputs used in the cost-effectiveness model are based upon the SHARP study comparing sorafenib to placebo. The SHARP trial (28) lasted only 72 weeks due to the statistically significant overall survival benefit seen at an interim analysis in the sorafenib treated group. Moreover, the trial did not follow all patients until death. As a result, extrapolation was necessary to determine the comparative effectiveness and cost-effectiveness beyond the duration of follow-up presented in the SHARP trial (28).

In order to be able to carry out a lifetime analysis, the efficacy parameters from the SHARP trial, TTP and OS had to be extrapolated to a 14 year time horizon, with the possibility of extending and reducing the time horizon in the sensitivity analysis (28).

The extrapolation assumes that, besides time, everything else remains constant. A natural way of carrying out the extrapolation is using the estimated parameters of the survival function. The assumption needed for this method is that survival times are drawn from the same distribution before and after the endpoint of the trial, for both comparators (68).

As patient level data from the SHARP trial (28) was available until the end of the follow-up (72 weeks), survival functions could be fitted on the existing dataset and Kaplan-Meier curves for both TTP and OS, using not only the averages, but the distribution of the data in time. Therefore, assuming that except for time, nothing else changed in the two patient populations, this led to the most accurate extrapolation.

TTP and OS were modelled for the two patient groups separately, choosing either the proportional hazards assumption, or the assumption, that the treatment effect has an effect on expected survival time. This way a separate survival regression was estimated for both treatment groups. A higher flexibility in modelling the survival was ensured by this method, since the shape parameter was not constrained to be the same for the two treatment arms. Having to estimate more parameters resulted in a slight loss of statistical degrees of freedom (increases the standard error of the estimates), but this disadvantage was offset by the higher flexibility, which led to better fit of the empirical Kaplan Meier survival curves and the parametrically fitted survival curves.

To choose among different distributions, the Akaike Information criterion (AIC) was used.

7.2.7 Clinical evidence

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The distributions used in the extrapolation were fitted separately to the two treatment arms, thus no baseline risk of disease progression was required.

7.2.7.2 How were the relative risks of disease progression estimated?

The distributions used in the extrapolation were fitted separately to the two treatment arms, thus estimation of the relative risk of disease progression was not required.

To estimate disease progression Weibull, lognormal, Gompertz, loglogistic and exponential approaches were fitted on the patient-level SHARP efficacy data and AIC (Akaike information criteria) was used as the measure of the goodness of fit. The AIC and the parameters for the chosen distribution were estimated outside MS Excel using a statistical package (STATA®). TTP and OS curves estimated with the help of the chosen distribution were calculated and compared diagrammatically to the Kaplan-Meier curves from the clinical trial. In addition medians from the model and the trial were compared for validity.

Ninety-five percent confidence intervals were used to conduct one-way sensitivity analysis around the effectiveness parameters, as well as a probabilistic sensitivity analysis. In the later, to incorporate the uncertainty surrounding the efficacy estimates Cholesky decomposition of the covariance matrix was employed (69), with the covariance matrix also estimated from the SHARP trial data (28).

The AIC showed that a lognormal model provided a significantly better fit than a Weibull, a loglogistic, an exponential, or a Gompertz distribution in the sorafenib group, and as good as the loglogistic distribution in the placebo group (see Appendix 10). The parameters of the lognormal curve, mu (const) and sigma, and the covariance matrices for TTP and OS for sorafenib and BSC for the Cholesky decomposition are also shown in Appendix 10.

The estimated TTP and OS curves were fitted to the observed KM survival estimates (and) from the trial, showing a good fit compared to the observed trial data.

Figure 6: Kaplan-Meier and Estimated Lognormal Curves for Sorafenib and BSC in Case of TTP According to Investigator Assessment

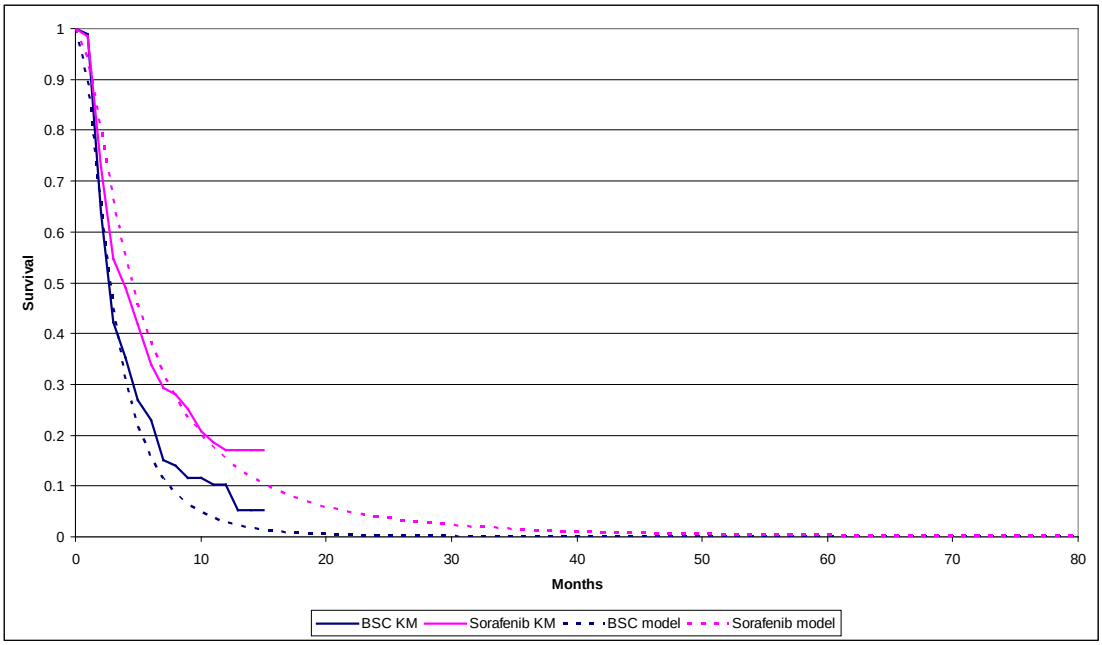
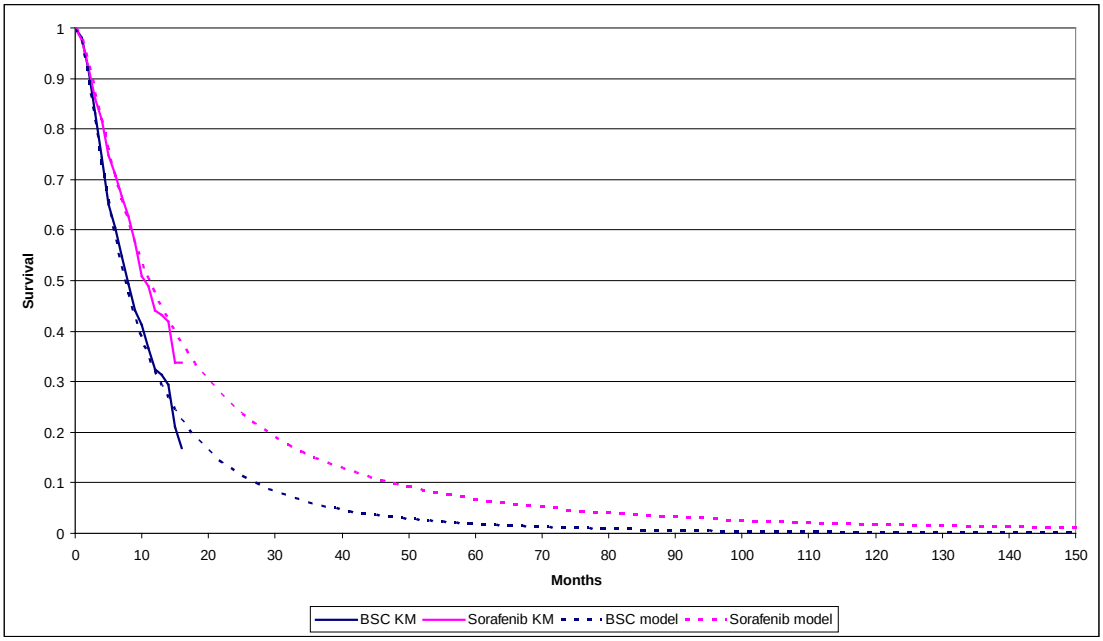


Figure 7: Kaplan-Meier and Estimated Lognormal Survival Curves for Sorafenib and BSC in case of OS



As a comparison to the trial results, approximately half (51.39% for sorafenib and 50.63% for BSC) of the patients progressed by 17 and 12 weeks (120 and 90 days) in the sorafenib and BSC arms of the model respectively, which compares well to the median TTP of 17 and 12 weeks for sorafenib and BSC respectively in the clinical trial.

Similarly, approximately half (50.29% for sorafenib, 50.62% for BSC) of the patients died by 47 weeks and 34 weeks (330 and 240 days) in the sorafenib and BSC arms of the model respectively, which also compares well to the median survival of 46 and 34 weeks for sorafenib and BSC respectively in the clinical trial.

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The outcomes included in the model were disease progression, overall survival and adverse events. These were taken from the SHARP trial (28). Using a utility mapping study utilities were assigned to these states and multiplied by the number of people in these states and the duration to calculate quality adjusted life years.

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Adverse event rates for sorafenib and BSC were derived from the SHARP clinical trial data. Adverse events were defined as any sign, symptom, illness, or diagnosis that appeared or worsened during the course of the study. The severity of adverse events was classified according to the NCI CTC (version 2.0) (49).

Based on the SHARP study, grade 3 or 4 adverse events (AEs) resulting from treatment were considered for inclusion in the model. Only those AEs reported in at least 10% of the sorafenib treated patients (Bayer data on file, CSR) and considered to have consequences for cost or patient quality of life by clinical experts were included in the analysis. The list and the number of AEs (Bayer data on file, CSR) (28) are tabulated below.

Table 19: Number of Adverse Events Observed in Trial (Grade 3 or 4 occurring in at least 10% of the sorafenib treated patients and assumed to have cost consequences)

	Sorafenib SHARP trial	BSC SHARP trial
Number of monthly cycles administered*	2335	2090
Sample size in trial	299	303
No. of events observed	160	118
Rash/desquamation	4	0
Hypertension	11	3
Fatigue	30	44
Weight loss	6	4
Alopecia	0	0
Diarrhoea	32	6
Nausea/vomiting	11	14
Hand-foot skin reaction	23	2
Pain abdomen	26	18
Haemorrhage, any event	17	27

*Because in the SHARP trial treatment cycle is 6 weeks the total number of patient months was estimated by dividing the number of patient days by 30 (28).

Grade 1 and 2 adverse events were mild and assumed to be treated with dose reductions and interruptions, and thus were not considered to have cost and utility consequences.

Table 20: Monthly Rates of Any Adverse Event

Treatment	Mean monthly rate	SD
Sorafenib	0.069	0.005
BSC	0.056	0.005

Table 20 shows the monthly rates for any of the AEs. The monthly (cycle) rates for sorafenib and BSC were calculated by dividing the number of grade 3 and 4 adverse events observed by the number of cycles administered. These AE rates were converted into probabilities of having any AE, and are applied to every cycle of the Markov model for all treatment states.

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

The clinical parameters were based on the patient-level data from the SHARP trial (28). Hence, expert opinion was not used to estimate any clinical parameters.

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

None, all of the model inputs and assumptions have been outlined in the preceding sections.

7.2.8 Measurement and valuation of health effects

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects were expressed as QALYs. However advanced HCC is a unique condition which poses methodological issues when evaluating the impact of new treatments on health related quality of life. Patients with hepatocellular carcinoma are heterogeneous, with a

diverse range of underlying causes of cirrhosis, including hepatitis B, hepatitis C, alcoholism and haemochromatosis. In some patients, typically younger women, HCC may develop where cirrhosis is not present. Due to this diverse liver disease, it is particularly difficult to disentangle the effect of the advanced HCC, underlying liver disease and interventions on quality of life. More specifically, quality of life is likely to be affected by the symptoms of the underlying liver disease, including liver failure, irrespective of whether the tumour has stabilised or regressed. As a result, it is not possible to demonstrate the impact of treatments in advanced HCC on quality of life, and no robust and reliable utility data is available that separates out the effect of the primary liver cancer from the underlying liver disease causes. For this reason health effects have also been expressed in terms of life years gained.

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Health effects measured and valued were progression free life years (PFLYs), life years (LYs), quality adjusted life years (QALYs) and AEs. The incidence and duration of these clinical inputs were derived from the data collected in the SHARP trial (28).

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

A search of the existing literature did not identify any relevant utility values for the model health states. A systematic review (Appendix 11) conducted by Bayer found 36 studies reporting utility weights for HCC. The utility values in the publications ranged between 0.10–0.95, and were mainly used in different subgroups of patients with hepatitis C or B or liver transplantation. Only Levy et al. (2008) (70) reported utility values for HCC without a specific subgroup of patients. They elicited utility values through standard gamble interviews with patients infected with chronic hepatitis B and uninfected responders. For uninfected patients the mean utility for HCC was 0.41 (95% CI: 0.39–0.43).

Although the study included a health state without hepatitis B, there are several issues that question the applicability of their results to the current HCC model. First, the description of the HCC health state in Levy et al. (2008) (70) assumes that some patients are taking chemotherapy, and experiencing AEs and additional hospital visits due to this therapy. In the model however the effect of AEs is taken into account separately (using AE-specific disutilities), and as an oral drug, sorafenib does not require additional visits for administration. Second, there was no time horizon set in the SG questions suggesting the interviewees might assume lifetime duration. Although the evidence suggests that the time horizon has a strong effect on values elicited by time trade-off (71), there is other evidence to suggest it would also influence SG results (72). Thirdly responders from Asia reported lower utilities, although this difference was not statistically significant in case of HCC (0.42 for UK vs. 0.31 for China). Lastly the Levy study did not distinguish between the health states included in the model (70). Thus the literature did not provide utility values for the relevant patient population but only for specific subgroups with a very wide range of utilities that do not differentiate between stable and progressive disease.

To derive utility scores that could be used in the economic evaluation the health-related quality of life (HRQL) as measured by the FACT-G part of Functional Assessment of Cancer Therapy— Hepatobiliary (FACT-HEP) instrument was mapped to time trade-off (TTO) utilities using an algorithm developed by Dobrez et al. (2007) (63). In the SHARP trial (28), the FACT-G (the general version of the cancer-specific HRQL measure) was used together with an additional subscale (FACT-Hep). The latter is a self-reported instrument designed to measure HRQL in patients with hepatobiliary cancers (42). The FACT-Hep consists of the 27-item FACT-G, which assesses generic HRQL concerns, and the newly validated 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues. Based on the algorithm by Dobrez et al. (2007)(63) four items from the FACT-G part of FACT-Hep were utilised to estimate utility scores. The algorithm developed by Dobrez et al. (2007) (63) was based on directly elicited TTO utilities provided by a large sample of cancer patients for their current health state and who also completed the FACT-G. A full copy of the utility mapping study is

presented in Appendix 12. Utility scores were obtained for first-line treatment with sorafenib and BSC before progression, and treatment with sorafenib and BSC after progression. These are consistent with the health states in the model, described in Section 7.2.6.2. Furthermore, utility values for the predefined treatment-related grade 3–4 toxicities were also estimated. The model accounts for the disutility of treatment resulting from selected grade 3 or 4 AEs. Table 21 presents the derived utility values.

Table 21: Utility Scores Derived from the Mapping Study

Before progression		
Sorafenib	Mean	0.69
	SD	0.12
BSC	Mean	0.69
	SD	0.12
After progression		
Sorafenib	Mean	0.71
	SD	0.13
BSC	Mean	0.71
after progression	SD	0.13
Disutility for AEs		
Sorafenib	Mean	-0.012
	SD	0.00
BSC	Mean	-0.012
	SD	0.00

The results of the mapping study found that the mean utility values derived from the mapping algorithm were similar between the different health states and treatment arms, and the definition of adverse events did not influence the results. Only marginal differences were identified between patients with stable HCC and patients with progressive disease, and between patients with and without adverse events. These between group differences were not significant. This might have been due to the fact, that the FACT-HEP values were collected relatively early in the SHARP trial (28) — at baseline and at the beginning of the third six weekly cycle, and the instrument not being sufficiently sensitive to pick up differences between these states.

The utility values for the different health states are multiplied in the model with the number of patients in the given health state at each cycle. The disutility values, obtained by subtracting the weighted average of the utility for all patients on sorafenib and BSC without the predefined adverse events from the weighted average of the utility values for all patients on sorafenib and BSC with the predefined adverse events, are then multiplied with the monthly probability of having any AE, and subtracted from the quality-adjusted life expectancy before progression at each cycle. The disutilities are only applied to health states before HCC progression. The derived utilities associated with progressive disease and advanced health states – and used in the model – already capture AEs resulting from treatment. Thus, to apply the monthly rates to these health states would double count the impact of AEs.

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 7.2.11).

The SHARP clinical trial did not include generic measures of quality of life. The results of the FACT-Hep data collected in the SHARP trial are presented in sections 6 and 7.2.8.3 (28).

7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

No health effects were excluded from the analysis.

7.2.9 Resource identification, measurement and valuation

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The model includes costs for drug treatment (sorafenib) for HCC and the treatment costs for the different health states and AEs. Resources included are the following:

- Drug costs for sorafenib and the treatment of AEs including:

    1. Sorafenib
    2. Ferrous sulphate
    3. Dexamethasone
    4. Loperamide
    5. Codeine
    6. Cyclizine
    7. Metoclopramide
    8. Domperidone
    9. Paracetamol
    10. Cholestyramine
    11. Atenolol
    12. Morphine sulphate

- Medical staff visits including:

    1. Oncologist
    2. Hepatologist
    3. Gastroenterologist
    4. Specialist nurse/Macmillan nurse
    5. Radiologist
    6. GP
    7. District nurse
    8. Palliative care team
    9. Specialist visit
    10. Dietician

- Laboratory and radiological tests

    1. 1. AFP Test
    2. Liver Function Test
    3. INR
    4. Complete blood count
    5. Complete metabolic panel/Biochemistry
    6. Microbiological examination
    7. IV rehydration
    8. Urea and electrolytes (blood urea nitrogen)
    9. Urea and electrolytes (urine)
    10. Endoscopy
    11. CT scan: abdominal
    12. MRI: abdominal
    13. Ultrasound: abdominal

- Inpatient costs including general ward and ICU and A&E admission

- Social care including home, day, hospice and residential care (included as a sensitivity analysis)

The cost estimates according to type of resource is shown in Table 22.

Table 22: Cost Estimates According to Type of Resource

Type of costs	Mean
Active treatment – routine care	
Hospitalisation	65
Medical staff visits	230
Lab tests	124
Radiological tests	61
Active treatment - after progression	
Hospitalisation	266
Medical staff visits	480
Lab tests	30
Radiological tests	78
BSC - first line	
Hospitalisation	151
Medical staff visits	225
Lab tests	124
Radiological tests	61
BSC – after progression	
Hospitalisation	386
Medical staff visits	364
Lab tests	30
Radiological tests	78
At progression - one off cost	
Hospitalisation	0
Medical staff visits	0
Lab tests	104
Radiological tests	134
End of life – one off cost	0

A detailed list is available together with the values used in Appendix 13

7.2.9.2 How were the resources measured?

In order to account for the costs associated with the management of patients with HCC and the treatment of AEs in the UK, resource use data was collected using expert opinion due to the absence of evidence from the published literature. In total, four interviews were conducted with leading UK clinical experts from the field of oncology and hepatology. All findings elicited from the resource use survey were based on the individual experiences and treatment practices of each of the physicians. Where required, the physicians provided best estimates of resource utilisation. A copy of the resource use survey is provided in Appendix 13.

All of the participating physicians have experience of sorafenib. The responses from each of the four physicians were subsequently collated and synthesised using descriptive statistics (i.e. the mean, standard deviation (SD)). Resource use data inputs and their associated costs are presented in Appendix 13. The data are arranged according to the health states and treatment phases used in the model: 1) first line – no progression with sorafenib, 2) progression (one off costs at the time of progression), 3) first line – no progression with BSC, 4) first-line treatment continued – post progression with sorafenib, and 5) BSC - post progression.

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

No, resource use was measured in separate study as described in section 7.2.9.2.

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Resources used to treat the end of life care are not included in the base case as every patient – regardless of the comparator (sorafenib or BSC) – has to pass through this state and there is no incremental difference in costs. A cost of palliative care is included as a sensitivity analysis.

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

All unit costs were obtained from public sources.

Unit costs were obtained from the following sources in order of preference:

- National Health Service (NHS) Reference Costs (73)
- Personal Social Services Research Unit (74)
- National Health Service Health and Social Care Information Centre (75)
- Where laboratory costs were not available for the NHS, the following sources were used:
    - Newcastle Upon Tyne 2006/07 tariffs (76)
    - Plymouth Hospital NHS trust 2008 (77)
    - UCL lab tariff 2007 (78)
    - Mullhaven Medical Laboratory 2008 (79)

Drug costs were extracted from the British National Formulary (BNF) (56).

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

Section 7.2.6.1 presents the monthly cost of sorafenib based on the mean daily dosage. In accordance with the SHARP trial(28) report, the mean daily dose is 710.5 mg/day which includes dose reductions and interruptions (section 7.2.1.1). This is equivalent to a monthly cost of £2,836.

The mean cost per month of sorafenib is calculated using the cost of £2,980.47 for 112, 200 mg tablets. The price per mg (calculated by dividing £2,980.47 by the number of tablets, 112, and dose, 200 mg) is multiplied by the average daily dosage, 710.5 mg, and the average number of days in a month, 30 days.

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure is required.

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Resources are measured and valued in a manner consistent with the reference case. However due to the lack of available evidence to accurately determine the costs of personal and social care these were included as a sensitivity analysis.

7.2.9.9 Were resource values indexed to the current price year?

Yes, resource values indexed to the current price year (2008).

7.2.9.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

The following assumptions were made regarding the estimation of resource measurement and valuation:

- As the SHARP trial (28) did not report resource use or costs and there was no evidence in the literature for costs of treating advanced HCC in the UK, these were collected separately using a UK resource use survey. Thus the assumption, that resource use based on a UK physician survey is representative of the treatment patterns in UK was made.

- All the unit costs were based on NHS costs apart from some laboratory tests, where NHS costs were not available.

- Costs did not differ for the various sub-groups, apart from the dose given, as these data were not available.

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Following the guidance specified in NICE's reference case, an annual discount rate of 3.5% was applied to both costs and health benefits occurring beyond the first year.

7.2.11 Sensitivity analysis

7.2.11.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The various sensitivity analyses have explored the main areas of uncertainty contained within the model. Elements of structural uncertainty have not been specifically explored. The model structure however is consistent with clinical practice and, together with the assumptions, was validated by clinical experts. It is also in line with other economic models developed in oncology, with the main health states of alive without cancer/progression, alive with cancer/progression and dead (64-67).

7.2.11.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

To explore uncertainty, one-way sensitivity analyses were conducted. The following scenario analyses are provided:

1. Discount rate: costs 0%, benefits 0%;
2. Discount rate: costs 6%, benefits 0%;
3. Discount rate: costs 0%, benefits 6%

4. Zero drug costs to estimate the cost-effectiveness of extending life alone in an end stage cancer disease;
5. Same patient management costs assuming that the cost of managing patients receiving sorafenib is equal to the costs of BSC, apart from drug costs, in all health states to estimate uncertainty associated with the elicited resource use data.
6. Inclusion of costs from assessment group report for RCC NICE appraisal assessment report to estimate uncertainty associated with the elicited resource use data
7. There was considerable uncertainty around the results for personal and social services costs elicited in the resource use survey due to variability in provision and funding between centres. These were therefore excluded from the basecase. Because of this a sensitivity analysis was conducted including social costs using different sources of data:
    a. Inclusion of PSS costs from the resource use survey
    b. Inclusion of end of life cost from the literature
8. Due to the high uncertainty surrounding the utility values, several scenario analyses were explored. Alternative utility assessment:
    a. In the base case utility scores for all patients with and without selected grade 3 and 4 adverse events are used. A sensitivity analysis was done with separate utility values for sorafenib and BSC.
    b. AEs disutility 0.05
    c. AEs disutility 0.2
    d. utility of 0.41 for all health states based on Levy et al. 2008 (70)
    e. no AE disutility, as in renal cell carcinoma, Bukowski et al (2007) (80) found no significant differences in quality of life between the sorafenib and the placebo (BSC) group
    f. utility values taken from the Renal Cell Carcinoma Assessment Report (81)
9. One of the assumptions in the model is that after progression 7.7% of the patients on sorafenib continue treatment for 129 days, as seen in the SHARP trial (28). Firstly the assumption that after progression patients on sorafenib would not be treated at all was tested and also the assumption that they would be treated for an additional 3 months.
10. In the model the time horizon was assumed to be lifetime (14 years) however it is important to test the impact of shorter time horizons. Thus time horizon was modified to:
    a. 2-years
    b. 5-years
    c. 10-years
11. As requested by the scope instead of TTP, time to symptomatic progression was used to define the ‘stable/no progression’ and the ‘progressed’ health states;
    a. With the help of the AIC criteria, the best fitting distribution was chosen separately for the two treatment arms and the appropriate parameters were calculated from the SHARP trial data (28).

One-way sensitivity analysis was also undertaken on all important parameters. The log-normal parameters for TTP and OS, mu and sigma, were varied according to 95% CI; utility estimated were varied according to the standard deviation, while for costs, in the absence of data, the extremes of mean +/- 30% were selected as reasonable upper and lower bounds.

7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Probabilistic sensitivity analyses of the key model parameters (time to progression, overall survival, adverse event rates, utility scores and management costs) were performed by sampling point estimates from the appropriate distributions.

Distributions were chosen on the basis of data applicability. For the probabilistic analysis, either a beta or gamma distribution was applied to the resource use data. Gamma distribution was applied to the cost data, whilst beta distribution was applied to the AEs rates for sorafenib and BSC as recommended by Briggs et al. (2006) (69). The lognormal parameters for efficacy parameters were made probabilistic with the help of Cholesky decomposition and the variance-covariance matrix generated from the patient level data (69).

Assumptions for the PSA are presented in tables 23-27 below.

Table 23: Efficacy Inputs

Base Case	**TTP**		**OS**	
	Mu	**Sigma**	**Mu**	**Sigma**
Sorafenib	4.822	0.983	5.791	1.147
BSC	4.513	0.804	5.465	1.019
Distribution	Lognormal	Lognormal	Lognormal	Lognormal

Source: SHARP trial (25)

Table 24: Lognormal Covariance Matrices for TTP and OS

	Sorafenib		**BSC**	
TTP				
	Const	ln sigma	Const	ln sigma
Const	0.004267	-	0.002534	-
ln sigma	0.000836	0.002994	0.000283	0.002373
OS				
	Const	ln sigma	Const	ln sigma
Const	0.007019	-	0.00449	-
ln sigma	0.002415	0.004141	0.001211	0.003221

Table 25: Utilities Input

Before progression		
Sorafenib	Mean	0.69
	SD	0.12
	Distribution	Beta
BSC	Mean	0.69
	SD	0.12
	Distribution	Beta
After progression		
Sorafenib	Mean	0.71
	SD	0.13
	Distribution	Beta
BSC	Mean	0.71
after progression	SD	0.13
	Distribution	Beta
Disutility for AEs		
Sorafenib	Mean	-0.012
	SD	0.00
	Distribution	Beta
BSC	Mean	-0.012
	SD	0.00
	Distribution	Beta

Table 26: Adverse events

	Mean	SD	Distribution	Alpha	Beta
Rates					
Sorafenib	0.069	0.005	Beta	160	2174.67
BSC	0.056	0.005	Beta	118	1972.23
Weighted cost per cycle (£)					
Sorafenib	133.62	40.09	Gamma	11.11	12.03
BSC	220.77	66.23	Gamma	11.11	19.87

Table 27: Cost Inputs (£)

Type of costs	Mean	SD	Distribution	Alpha	Beta	Source
Active treatment – routine care						
Hospitalisation	65	19.43	Gamma	11.11	5.83	Expert Opinion
Medical staff visits	230	69.10	Gamma	11.11	20.73	Expert Opinion
Lab tests	124	37.24	Gamma	11.11	11.17	Expert Opinion
Radiological tests	61	18.22	Gamma	11.11	5.47	Expert Opinion
Active treatment - after progression						
Hospitalisation	266	79.87	Gamma	11.11	23.96	Expert Opinion
Medical staff visits	480	143.88	Gamma	11.11	43.16	Expert Opinion
Lab tests	30	9.11	Gamma	11.11	2.73	Expert Opinion
Radiological tests	78	23.44	Gamma	11.11	7.03	Expert Opinion
BSC - first line						
Hospitalisation	151	45.36	Gamma	11.11	13.61	Expert Opinion
Medical staff visits	225	67.61	Gamma	11.11	20.28	Expert Opinion
Lab tests	124	37.24	Gamma	11.11	11.17	Expert Opinion
Radiological tests	61	18.22	Gamma	11.11	5.47	Expert Opinion
BSC – after progression						
Hospitalisation	386	115.77	Gamma	11.11	34.73	Expert Opinion
Medical staff visits	364	109.34	Gamma	11.11	32.80	Expert Opinion
Lab tests	30	9.11	Gamma	11.11	2.73	Expert Opinion
Radiological tests	78	23.44	Gamma	11.11	7.03	Expert Opinion

Type of costs	Mean	SD	Distribution	Alpha	Beta	Source
At progression - one off cost						
Hospitalisation	0	0.00	Gamma	NA	NA	Expert Opinion
Medical staff visits	0	0.00	Gamma	NA	NA	Expert Opinion
Lab tests	104	31.34	Gamma	11.11	9.40	Expert Opinion
Radiological tests	134	40.09	Gamma	11.11	12.03	Expert Opinion
End of life – one off cost	0	0	Gamma	NA	NA	NA

Details of the resource use and unit costs can be found in Appendix 13.

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

The transition probabilities to progression or death were calculated with the help of lognormal parameters, mu (const) and sigma depending on the number of months passed after the start of therapy and hence changes for each cycle (see section 7.2.7.2). Adverse event rates were transformed into transition probabilities using the following formula: 1-exp(-mean rate).

7.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

HCC is a progressive disease; therefore both TTP and OS vary over time. This time dependency was taken into account with the use of the lognormal distribution (see section 7.2.7.2).

AEs in the model are assumed time-independent. In clinical practice, AEs are likely to be experienced at different stages of treatment, particularly on initiation and then tachyphylaxis develops to the AE or they resolve following dose reduction. Hence, the assumption of uniformity is likely to overestimate the occurrence of AEs when treated with sorafenib.

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The face validity was examined by presenting the model structure, data sources, assumptions and other design aspects to clinical experts at an advisory board. Furthermore median TTP and OS from the model were compared with the results from the SHARP trial (3). The technical validity of the model was tested internally to ensure that calculations were correct and that the results were logical and consistent. This was conducted by several analysts, by examining formulae and conducting one and two-way sensitivity analyses.

7.3 Results

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

Figures 8 and 9 show the distribution of patients treated with sorafenib and BSC respectively.

Figure 8: Distribution of patients treated with sorafenib

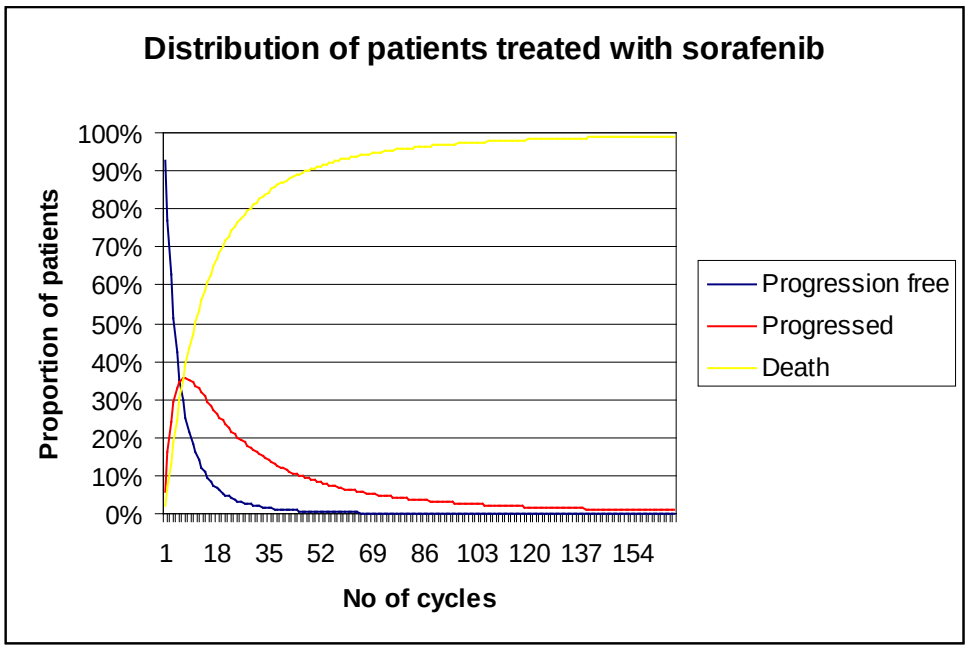
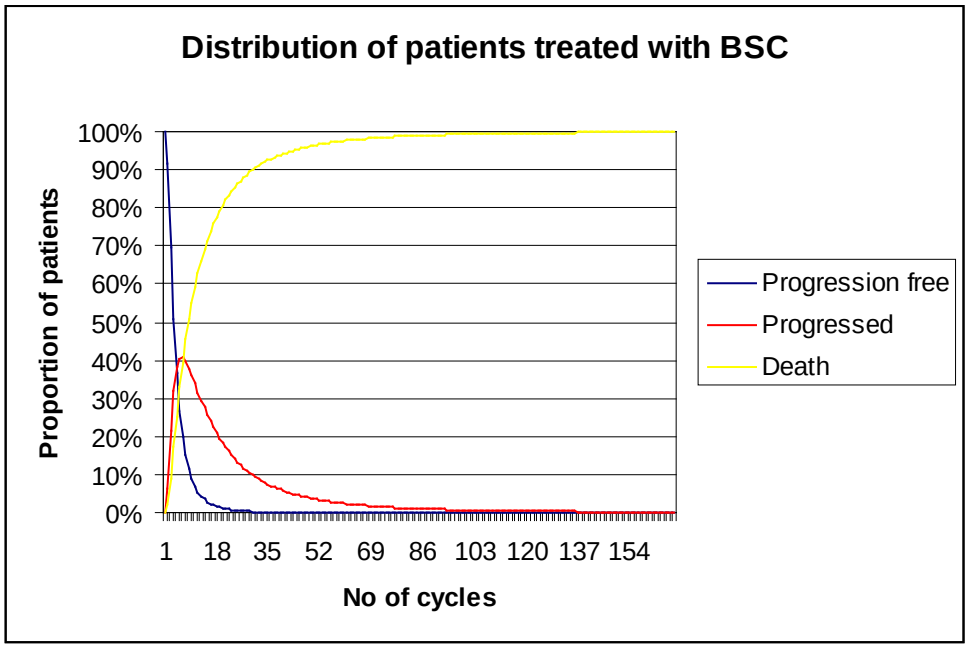


Figure 9: Distribution of patients treated with BSC



The base case analysis is presented in Table 28. The model indicates that the total discounted costs over a lifetime for a patient on sorafenib are £32,971 while the costs for best supportive care are £9,739. The undiscounted cost break down by phase is shown graphically in Figure 10. The improved clinical outcomes with sorafenib result in estimated discounted QALYs of 1.08 versus 0.72 with BSC. The incremental difference in costs and QALYs results in an ICER of £64,754. The estimated LYs gained is 1.54 for sorafenib compared to 1.03 for BSC resulting in an incremental cost per life year gained of £45,502.

Table 28: Base Case Results

Per Patient	LYG	QALYs	Total Costs (£)	ICER	
				Cost/LYG (£)	Cost/QALY (£)
Sorafenib	1.54	1.08	**32,971**	**45,502**	**64,754**
BSC	1.03	0.72	**9,739**		

Costs and benefits discounted 3.5%

Figure 10: Cost Breakdown by Phase (Undiscounted Results)

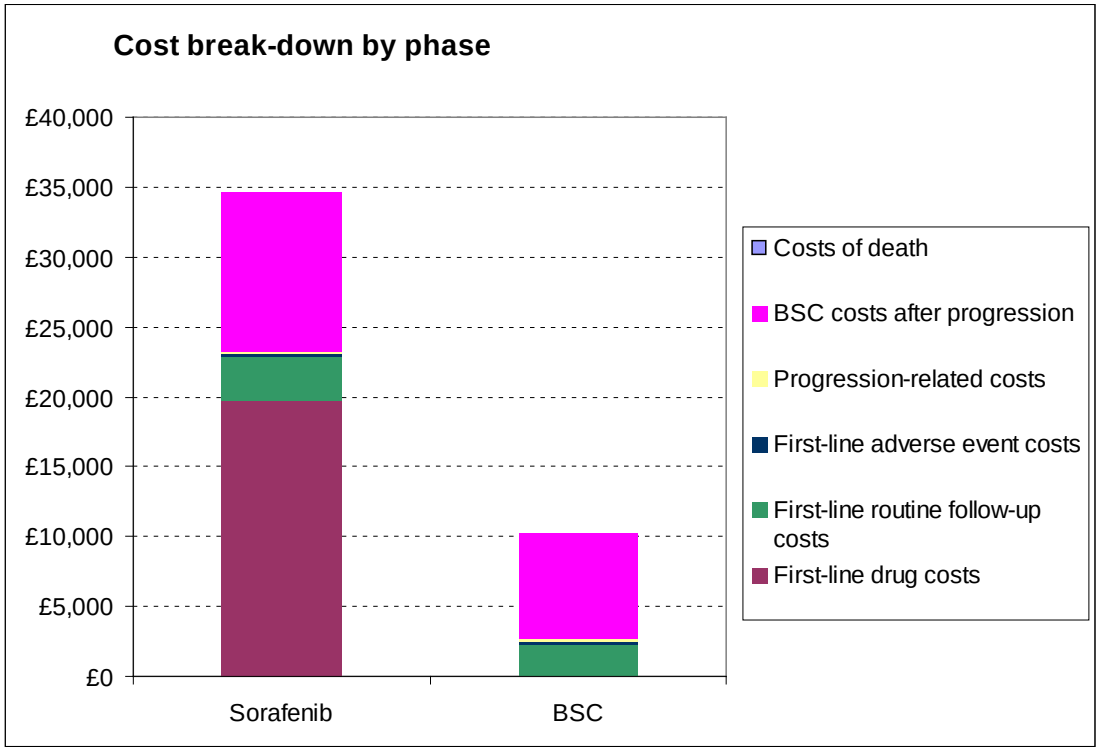


Table 29: Cost breakdown by phase

First-line treatment	Sorafenib	BSC
Total costs (discounted)	**£32,971**	**£9,739**
Total costs (undiscounted)	£34,661	£10,262
Break-down by phase (undiscounted)		
First-line drug costs	£19,673	0
First-line routine follow-up costs	£3,171	£2,322
First-line adverse event costs	£216	£208
Progression-related costs	£144	£156
BSC costs after progression	£11,457	£7,576
Costs of death	0	0

7.2.14 Subgroup analysis

7.2.14.1 What were the results of the subgroup analysis/analyses if conducted?

In addition to the base case analysis, a series of subgroups were considered. Using the lognormal distribution, TTP and OS for the various subgroups was predicted based on investigator assessment (see Section section 7.2.7.2). The results from the subgroup analyses are tabulated below.

Table 30: Results from Subgroup Analyses

	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG(£)	Cost/ QALY(£)
Total Population (base case)	0.51	0.36	23,232	**45,502**	**64,754**
Age =>65	0.78	0.55	27,788	**35,474**	**50,364**
Child Pugh A	0.47	0.33	22,376	**47,355**	**67,396**
TNM I-III	1.32	0.94	32,453	**24,507**	**34,641**
BCLC Stage C	0.43	0.30	22,827	**53,549**	**76,592**
BCLC Stage B	1.26	0.89	29,229	**23,236**	**32,701**
[redacted]					

Costs and benefits discounted 3.5%

The results from the subgroup analysis show that the incremental costs-effectiveness ratios ranged from £23,236 (BCLC Stage B) to £56,141 [redacted] for cost/LYG and £32,701 (BCLC Stage B) to £80,198 [redacted] for cost/QALY. BCLC stage B, TNM I-III [redacted] subgroups had the most favourable results.

7.2.15 Sensitivity analyses

7.2.15.1 What were the main findings of the sensitivity analyses?

Changing the utility values, the method of identifying progression, the drug costs and the time horizon has a significant effect on the results, while the modification of the management costs and the disutilities have a limited influence on the results (Table 31).

Table 31: Scenario Analysis Discounted Results

Analyses description	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG (£)	Cost/QALY (£)
Base Case	0.51	0.36	23,232	45,502	64,754
Discount rates					
Discount rate: costs 0%, benefits 0%;	0.58	0.41	24,399	41,883	59,545
Discount rate: costs 6%, benefits 0%;	0.58	0.41	22,524	38,666	54,972
Discount rate: costs 0%, benefits 6%	0.47	0.33	24,399	52,040	74,108
Cost data					
Zero drug costs	0.51	0.36	4,029	7,891	11,230
Same patient management costs	0.51	0.36	23,759	46,533	66,221
Management costs taken from the RCC assessment report^	0.51	0.36	21,158	41,440	58,973
Inclusion of PSS costs	0.51	0.36	24,249	47,494	67,589
Cost of death included *(£3,923)	0.51	0.36	23,147	45,334	64,515
Alternative utility assessment					
a) Separate Sorafenib and BSC**	0.51	0.36	23,232	45,502	63,739
b) AEs disutility 0.05	0.51	0.36	23,232	45,502	64,930
c) AEs disutility 0.2	0.51	0.36	23,232	45,502	65,380
d) Utility of 0.41 for all health states	0.51	0.21	23,232	45,502	110,904
e) No AE disutility	0.51	0.36	23,232	45,502	64,780
f) Utilities from RCC assessment report~~	0.51	0.36	23,232	45,502	63,992
Length of sorafenib treatment after progression					
0 months	0.51	0.36	22,296	43,668	62,144
3 months	0.51	0.36	22,949	44,948	63,965
Time horizon					
2 years	0.19	0.13	18,844	97,962	141,425
5 years	0.38	0.27	21,779	56,833	81,171
10 years	0.48	0.34	22,945	47,420	67,526

Analyses description	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG (£)	Cost/QALY (£)
Outcomes assessment					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG= life-years gained, TTSP: time to symptomatic progression
*Assumed a cost of £3,923, taken from Coyle et al (1999), averaged over hospital and hospice stays = £2,701, revalued to 2007/8
**Using the following mapped utilities: First line – no progression with sorafenib: 0.6957, First-line treatment continued – post progression with sorafenib: 0.7132, First line – no progression with BSC: 0.6818, BSC - post progression: 0.7094 (see Appendix 12)
[(81)]^Assumed a 6-weekly cost of £81 and £223 for BSC and drug treatment before progression respectively, and £435 for progressive disease independent of the treatment (table 41 in the Renal Cell Carcinoma NICE Assessment Report).
~~[(81)] Utilities for Sorafenib and BSC Before progression equated to 0.76 and utilities after progression equated to 0.68 (table 37 in the Renal Cell Carcinoma NICE Assessment Report)

One-way deterministic sensitivity analysis was performed where efficacy parameters were varied according to 95% confidence intervals, utilities according to standard deviation, and disutility estimates and costs by ±30% The most influential factors in the model were estimates for TTP and OS from the SHARP trial (3) together with the utility values,

Probabilistic sensitivity analyses for sorafenib vs. BSC
Results of the probabilistic sensitivity analyses for sorafenib vs. BSC are presented in Table 32. The results on the cost-effectiveness plane and the cost-effectiveness acceptability curves are shown in Figure 11 to 14 respectively.

Table 32: Probabilistic Sensitivity Analysis for Sorafenib vs. BSC

First-line treatment		Sorafenib	BSC	Incremental
Total costs (discounted) (£)	Probabilistic Mean	**33,085**	**9,778**	23,307
	Standard Deviation	3,048	1,730	
	2.5% and 97.5% percentile	27,463 to 39,631	6,901 to 13,679	
LY gained	Probabilistic Mean	**1.55**	**1.04**	0.52
	Standard Deviation	0.17	0.09	
	2.5% and 97.5% percentile	1.25 to 1.90	0.87 to 1.22	
QALYs	Probabilistic Mean	**1.09**	**0.73**	0.36
	Standard Deviation	0.19	0.12	
	2.5% and 97.5% percentile	0.74 to 1.47	0.51 to 0.95	
Incremental cost (*£)* per LY gained				**45,832**
Incremental cost (*£)* per QALY				**65,244**

Figure 11: Probabilistic Analysis - Results on the Cost-Effectiveness Plane, BSC vs. Sorafenib, Cost per QALY

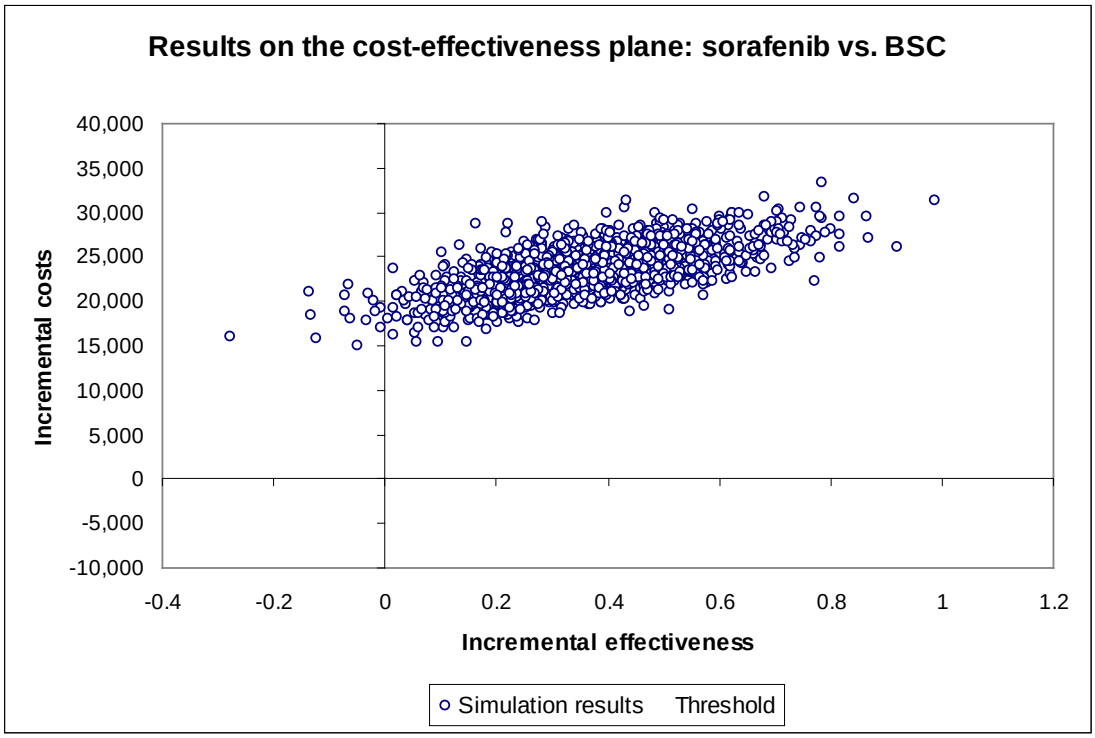


Figure 12: Probabilistic Analysis - Results on the Cost-Effectiveness Plane, BSC vs. Sorafenib, Cost per LY

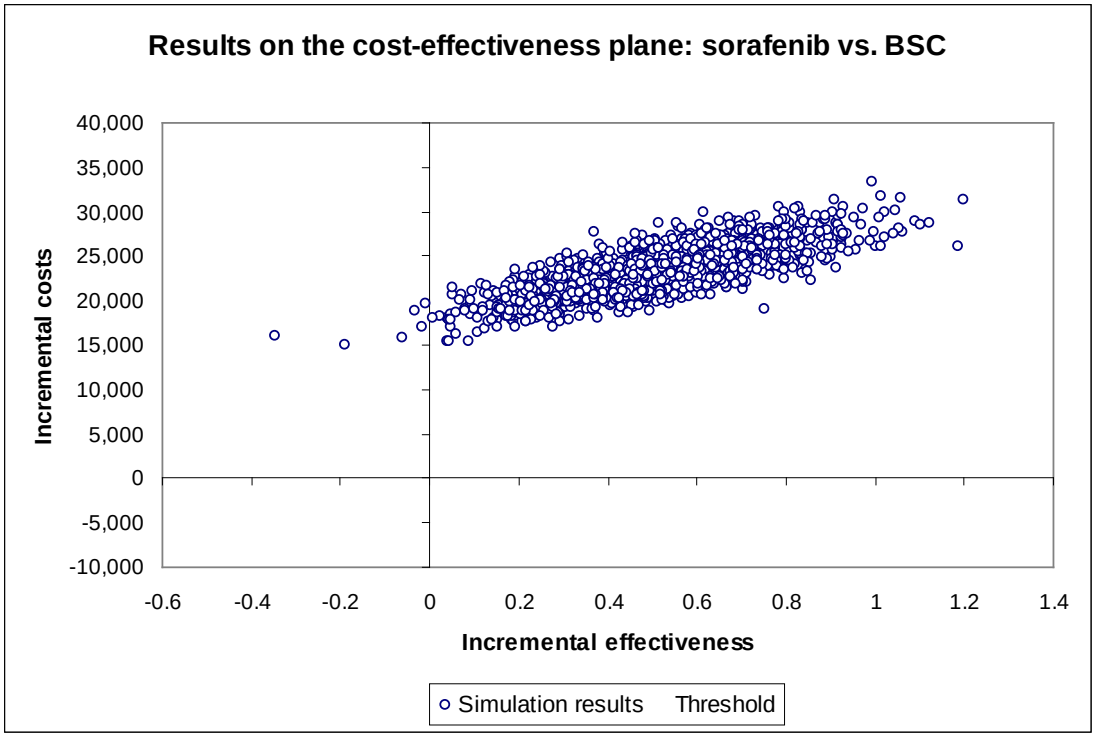


Figure 13: Probabilistic Analysis, CEAC for BSC vs. Sorafenib, Cost per QALY

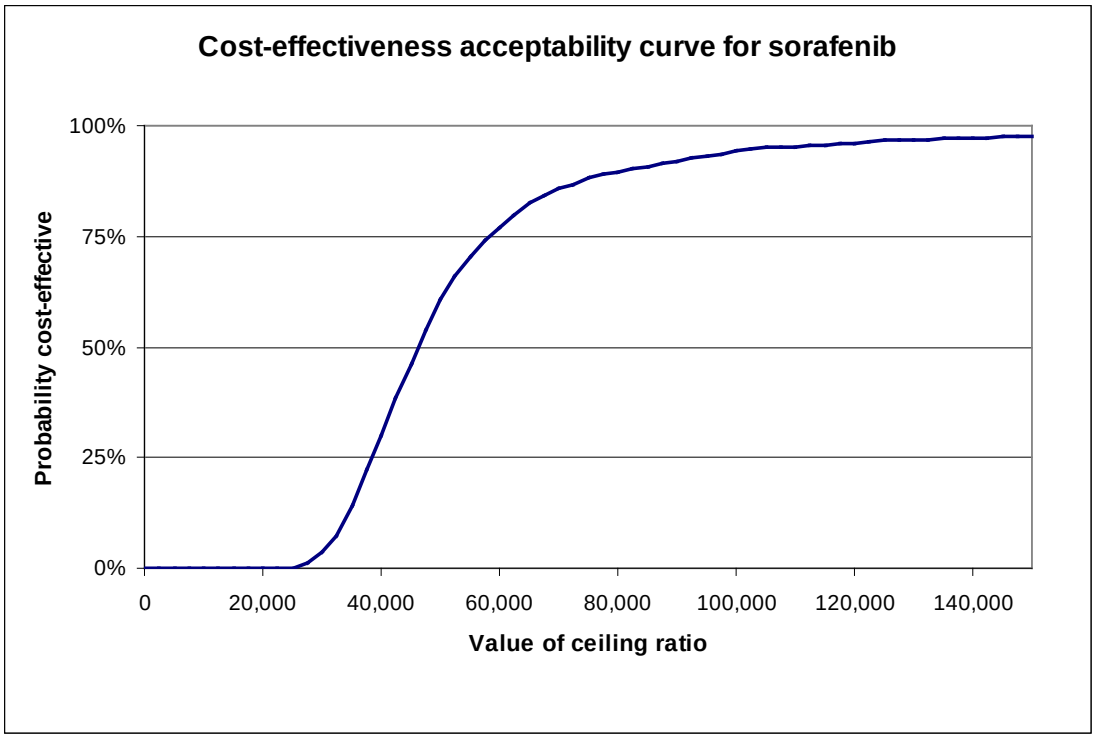
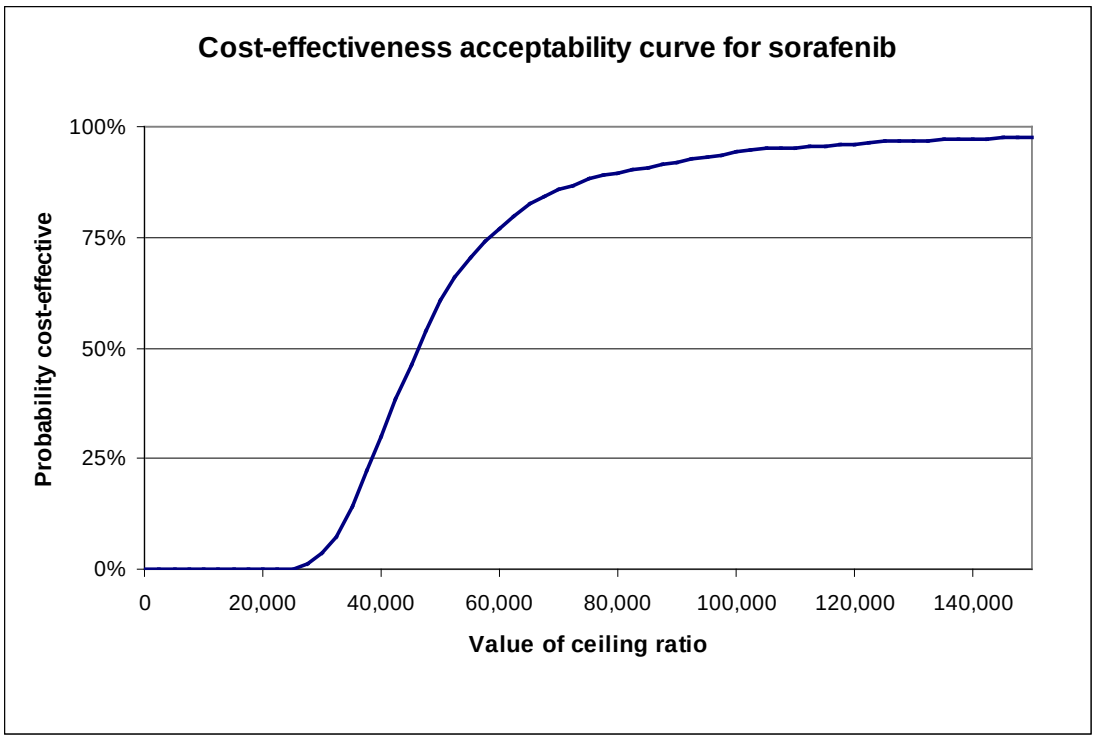


Figure 14: Probabilistic Analysis, CEAC for BSC vs. Sorafenib, Cost per LY gained



7.2.15.2 What are the key drivers of the cost effectiveness results?

The key driver of the cost-effectiveness results as seen in section 7.3.3.1 are the estimates for TTP and OS from the SHARP trial (3) together with the utility values, which are surrounded by high uncertainty due to the methodological problems associated with valuing quality of life in this heterogeneous disease. For this reason the cost per life years gained figures have also been presented.

7.2.16 Interpretation of economic evidence

7.2.16.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

A systematic review of the economic literature (22) did not identify any published economic evaluations for sorafenib in HCC relevant to the UK.

7.2.16.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

It is believed that the results of this economic evaluation are highly relevant to advanced HCC patients in England and Wales because:

- The underlying disease and demographics of the subjects in the patient groups used for the modelling are unlikely to differ from patients in England and Wales;
- UK experts in HCC were consulted on key assumptions and methods used in the model;
- Medical resource use estimates and unit costs were based on UK sources.

7.2.16.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The strengths of the model include:

- The model structure is consistent with clinical practice and other economic models in oncology.
- The model follows a simple structure for transparency and interpretability while conceptualising the disease by its clinical milestones such as disease progression and death following progression, which are the most important outcomes in the disease and SHARP trial (3).
- The face validity was examined by presenting the model structure, data sources, assumptions and other design aspects to clinical experts at an advisory board. Furthermore median TTP and OS from the model were compared with the results from the SHARP trial (3). Both the median OS and TTP compared well to the median respective values in the SHARP trial (3)(see section 7.2.7.2) The technical validity of the model was tested internally to ensure that calculations were correct and that the results were logical and consistent. This was conducted by several analysts, by examining formulae and conducting one and two-way sensitivity analyses.

Data constraints lead to the following limitations:

- First, with most economic models, the analysis was based on multiple data sources and analytical assumptions. Because the SHARP trial (3) demonstrated a statistically significant increase in overall survival at 72 weeks and was consequently stopped

early, the patient-level efficacy data were extrapolated by fitting a distribution to the patient level data. As demonstrated in deterministic sensitivity analysis, these efficacy parameters were the most important model drivers.

- A second limitation of the study is that the model relied on expert opinion to estimate resource consumption for management of HCC and AEs related to treatment. However, in the absence of available resource use data for management of HCC this is recognised as the next best approach. At the same time — with the exception of BSC after progression — costs had only a marginal effect on the results according to the sensitivity analysis. Obtaining real-life data for these parameters would strengthen the overall validity of the model.

- A third limitation concerns the utilities used in the model. A search of the existing literature did not identify any relevant utility values for the model health states. A highly variable range of utility values was found in the literature, which did not match the health states in the model or trial population. Because utilities were not directly measured in the SHARP trial (3) and the systematic literature review did not report any relevant utility values these had to be estimated thorough a mapping study. It is recognised that the validity of these results may be limited by the timing of the quality of life assessment and the sensitivity of the instrument used Since more reliable utility estimates are not available for advanced HCC, results in terms of LY gained would more accurately represent the cost effectiveness of sorafenib rather that the increment cost per QALY measure (see section 7.2.8.3)

It should also be noted that the evaluation employed a set of conservative assumptions around AEs. All AEs were assumed to be constant throughout the model. In clinical practice, AEs are likely to be experienced at different stages of treatment, particularly on initiation and then tachyphylaxis develops to the AE or they resolve following dose reduction. Hence, the assumption of uniformity is likely to overestimate the occurrence of AEs when treated with sorafenib.

7.2.16.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As described above, a systematic review of utility in HCC found no suitable utility values for the model HCC health states. The literature review reported a wide range of utility values, which did not distinguish progressive from stable disease. Furthermore, these utility values were mainly for specific subgroups and not relevant to the patient population used in the current analysis.

HCC is a unique condition which poses methodological issues when evaluating the impact of new treatments on health related quality of life. Patients with HCC are heterogeneous, with a diverse range of underlying causes of chirrosis. As a result it is particularly difficult to disentangle the effect of the advanced HCC, underlying live disease and interventions on quality of life. The heterogeneous co morbidity profile affects the patients prognosis, quality of life and treatment. Given that this is an end of life medicine, with small patient numbers, a demonstrable survival benefit and no alternative treatments, sorafenib should be considered under the End of Life Policy (12).

Applying a single estimate of cost-effectiveness to the overall advanced HCC group of patients is unreliable because of the unique large variation in underlying disease (e.g., liver cirrhosis), rarely seen in other cancers, it is therefore of utmost importance to base decisions on patient sub-groups where the health and economic outcomes are most likely to vary considerably from the overall mean.

It is acknowledged there is a high degree of variability around the point estimate of cost effectiveness due to the heterogeneous nature of the disease and the difficulty disentangling the underlying liver disease and treatment effects. For these reasons, it would be appropriate to collect further evidence as recommended under the end of life scheme.

8. Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales resulting from the introduction of sorafenib is shown in table 33. The budget impact analysis shows a total of 1726-2416 patients will be treated with sorafenib over the next 5 years according to the projected market share and the proportion of patients eligible for treatment.

The budget impact — assuming patients continue to receive only BSC — was calculated to be approximately £29 million compared with approximately £60 million with the introduction of sorafenib using the lower bracket of 25% patients eligible for treatment, while the budget impact was calculated to be approximately £41 million compared with roughly £85 million with the introduction of sorafenib using the upper bracket of 35% patients eligible for treatment. This resulted in a net budget impact of approximately £31-44 million. Based on drug cost only, this represents an increase of £29 million to £41million respectively using 25% and 35% patients eligible for treatment over the next 5 years for the NHS in England and Wales.

Table 33: Budget Impact Results for the Base Case (Total population) (with the lower bracket of 25%)

Year	1	2	3	4	5	Total
Budget impact with BSC only	3,718,243	5,287,678	6,108,507	6,652,114	7,067,137	28,833,679
Budget impact with projected market shares for sorafenib						
Drug costs	1,571,524	3,502,271	5,629,471	7,929,924	10,382,317	29,015,508
Management costs	3,715,510	5,386,369	6,407,574	7,235,015	8,006,061	30,750,529
Total Costs	5,287,035	8,888,641	12,037,045	15,164,938	18,388,378	59,766,037
Difference						
Drug costs	1,571,524	3,502,271	5,629,471	7,929,924	10,382,317	29,015,508
Management costs	-2,733	98,691	299,066	582,901	938,924	1,916,850
Total Costs	1,568,792	3,600,963	5,928,538	8,512,824	11,321,242	30,932,358

8.2 What numbers of patients were assumed to be eligible? How was this figure derived?

The tables below provided a step by step explanation of how the eligible patient population was derived.

Step 1: Raw data

According to ICD-10 code C22.0 (Liver cell carcinoma including hepatocellular carcinoma and hepatoma) from Cancer Research UK there were 2,751 new cases of liver cancer diagnosed in 2005(1).

Table 34: Number of new cases and rates for liver cancer UK 2005

	England	Wales	Total
Males	1,599	95	1,694
Females	985	72	1,057
Total	2,584	167	2,751

Source: Cancer Research UK 2008 (1)

Step 2: Increase of incidence

Assuming a constant increase in the future for England and Wales(1) , the average increase in incidence for both females and males in England over the past five years was used to calculate the trend associated with the increase in the liver cell carcinoma (5)

Table 35: Increase of Incidence in England

Year	Incidence		Increase	
	Males	Females	Males	Females
2002	1357	891	NA	NA
2003	1368	833	0.0080	-0.0696
2004	1385	947	0.0123	0.1204
2005	1599	985	0.1338	0.0386
2006	1621	950	0.0136	-0.0368
Average increase rate			0.0419	0.0131

Source: Cancer Research UK 2008(1)

Step 3: Forecast with increasing incidence

Table 36: Forecast with Increasing Incidence for England and Wales

Forecast incidence	Males	Females	Total
2005	1694	1057	2751
2006	1765	1071	2836
2007	1839	1085	2924
2008	1916	1099	3015
2009	1996	1114	3110
2010	2080	1128	3208
2011	2167	1143	3310
2012	2258	1158	3416
2013	2353	1173	3526

Step 4: Estimating incidence HCC

The ICD-10 C22.0 code used for liver cell carcinoma includes hepatocellular carcinoma and hepatoma. Based on Wilson 2005, 80%–90% of liver cancer patients are suffering from HCC (26), thus 85% was used as an average.

Table 37: Number of patients in England and Wales with HCC

Forecast incidence	Males	Females	Total
2009	1697	947	2644
2010	1768	959	2727
2011	1842	972	2814
2012	1920	984	2904
2013	2000	997	2997

Step 5: Estimation of the eligible patient population

Of all HCC patients, those with advanced stage disease who have failed or are unsuitable for surgical or locoregional therapies and will be eligible for sorafenib comprise only 25%–35% (2) of the patients. Hence, the incident eligible sub-populations equals 661–749 patients using the lower bracket and 925 to 1049 patient using the upper bracket.

Table 38: Number of Eligible Patients (using the lower bracket of 25%)

	Males	Females	Total
Forecast incidence			
2009	424	237	661
2010	442	240	682
2011	461	243	703
2012	480	246	726
2013	500	249	749

Table 39 Number of Eligible Patients (using the upper bracket of 35%)

	Males	Females	Total
Forecast incidence			
2009	594	331	925
2010	619	336	954
2011	645	340	985
2012	672	345	1016
2013	700	349	1049

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

No active treatments other than sorafenib are available in advanced HCC. Patients are assumed to currently receive BSC.

8.4 What assumption(s) were made about market share (where relevant)?

As sorafenib is the only treatment showing statistically significant overall survival, the current market share is 0% and in the following years it is assumed this will increase up to 80% of the eligible population.

Table 40: Projected market share for Total population

Drug	Current status	Year 1	Year 2	Year 3	Year 4	Year 5
Sorafanib	0%	16%	32%	48%	64%	80%
BCS	100%	84%	68%	52%	36%	20%

8.5 What unit costs were assumed? How were these calculated?

The costs for the budget impact model are derived from the cost effectiveness model. Patients starting on BSC incur costs of £5,657 in their first year, £2,237 in year two and totalling £9,771 by year five. Patients starting on sorafenib will incur total costs of £20,627 in their first year (annual drug cost will be £15,008), £5,742 (annual drug cost will be £2,521) in year 2 and totalling £31,593 (total drug cost will be £18,791) by year five. The annual cost calculation takes into account the fact that the probability of a single patient staying eligible for sorafenib is 100%, 13.9%, 3.7%, 1.4% and 0.6% in the next five years.

Table 41: Annual Total and Drug Cost for Sorafenib and BSC per patient

Total annual costs	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Sorafenib	20,558	6,316	3,113	1,854	1,221	33,063
BSC	5,897	2,632	1,314	750	467	11,060
Annual drug cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Sorafenib	14,693	2,744	921	402	203	18,964
BSC	0	0	0	0	0	0

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

The analysis calculates the budget impact for sorafenib based on the cost-effectiveness model, estimating the uptake of sorafenib compared to BSC based on drug cost only and for total health care costs which include routine follow-up costs, hospitalisations and the managements of AEs. These are presented in section 6.

8.7 Were there any estimates of resource savings? If so, what were they?

No direct resource or cost savings are anticipated.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

NA

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10 Appendices

See document: Nexavar HCC_STA form_Appendices_confidential.doc

Single Technology Appraisal (STA) of sorafenib (Nexavar®) for the treatment of hepatocellular carcinoma (HCC)

Appendices

14th January 2009

Please note confidential information has been removed from this document

List of appendices

Appendices

10.1 Appendix 1: Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Nexavar 200 mg film-coated tablets▼

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of sorafenib (as tosylate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Red, round, biconvex film-coated tablets, debossed with Bayer cross on one side and "200" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hepatocellular carcinoma
Nexavar is indicated for the treatment of hepatocellular carcinoma (see section 5.1).

Renal cell carcinoma
Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

4.2 Posology and method of administration

Nexavar treatment should be supervised by a physician experienced in the use of anticancer therapies. The recommended dose of Nexavar in adults is 400 mg (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg). It is recommended that sorafenib should be administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Posology adjustments:
Management of suspected adverse drug reactions may require temporary interruption or dose reduction of Nexavar therapy. When dose reduction is necessary, the Nexavar dose should be reduced to two tablets of 200 mg once daily (see section 4.4).

Paediatric patients: The safety and efficacy in children and adolescents (< 18 years) have not been studied. Nexavar is not recommended for use in children and adolescents due to a lack of data on safety and efficacy (see section 5.3).

Elderly patients: No dose adjustment is required in the elderly (patients above 65 years of age).

Renal impairment: No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis (see section 5.2).

Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

Hepatic impairment: No dose adjustment is required in patients with Child Pugh A and B (mild to moderate) hepatic impairment. No data is available on patients with Child Pugh C (severe) hepatic impairment (see section 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Dermatological toxicities: Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with Nexavar. Rash and hand-foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with Nexavar. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of Nexavar, or in severe or persistent cases, permanent discontinuation of Nexavar (see section 4.8).

Hypertension: An increased incidence of arterial hypertension was observed in Nexavar-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of Nexavar should be considered (see section 4.8).

Haemorrhage: An increased risk of bleeding may occur following Nexavar administration. If any bleeding event necessitates medical intervention it is recommended that permanent discontinuation of Nexavar should be considered (see section 4.8).

Cardiac ischaemia and/or infarction: In a randomised, placebo-controlled, double-blind study (study 1, see section 5.1) the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the Nexavar group (2.9%) compared with the placebo group (0.4%). In study 3 (see section 5.1), the incidence of treatment-emergent cardiac ischaemia/infarction events was 2.7% in Nexavar patients compared with 1.3% in the placebo group. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from these studies. Temporary or permanent discontinuation of Nexavar should be considered in patients who develop cardiac ischaemia and/or infarction (see section 4.8).

Gastrointestinal perforation: Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking sorafenib. In some cases this was not associated with apparent intra-abdominal tumor. Sorafenib therapy should be discontinued (see section 4.8).

Hepatic impairment: No data is available on patients with Child Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated via the hepatic route exposure might be increased in patients with severe hepatic impairment (see section 4.2 and 5.2).

Warfarin co-administration: Infrequent bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on Nexavar therapy. Patients taking concomitant warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes (see sections 4.5 and 4.8).

Wound healing complications: No formal studies of the effect of sorafenib on wound healing have been conducted. Temporary interruption of Nexavar therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume Nexavar therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing.

Elderly: The experience with the use of Nexavar in elderly patients is limited. Cases of renal failure have been reported. Monitoring of renal function should be considered.

Renal cell carcinoma: High Risk Patients, according to MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the phase III clinical study in renal cell carcinoma (see study 1 in section 5.1); and benefit-risk in these patients has not been evaluated.

Drug-drug interactions:
Caution is recommended when administering Nexavar with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. irinotecan) or UGT1A9 pathways (see section 4.5).

Caution is recommended when sorafenib is co-administered with docetaxel (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Inducers of metabolic enzymes: Administration of rifampicin for 5 days before administration of a single dose of sorafenib resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity and/or glucuronidation (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.

CYP3A4 inhibitors: Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. These data suggest that clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

CYP2C9 substrates: Sorafenib inhibited CYP2C9 *in vitro*. It cannot be excluded that sorafenib may increase the concentrations of concomitantly administered substrates of CYP2C9. The concomitant treatment with Nexavar and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. However, patients taking warfarin or phenprocoumon should have their INR checked regularly (see section 4.4).

CYP2B6 and CYP2C8 substrates: Sorafenib inhibited CYP2B6 and CYP2C8 *in vitro*, but the clinical relevance of this inhibition has not been evaluated. It cannot be excluded that sorafenib may increase the concentrations of concomitantly administered substrates of CYP2B6 (e.g. bupropion, cyclophosphamide, efavirenz, ifosfamide, methadone) and CYP2C8 (e.g. paclitaxel, amodiaquine, repaglinide).

UGT1A1 and UGT1A9 substrates: *In vitro*, sorafenib inhibited glucuronidation via UGT1A1 and UGT1A9. The clinical relevance of this finding is unknown (see below and section 4.4).

CYP isoforms selective substrates: Concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19 respectively, did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are unlikely.

In vitro studies of CYP enzyme induction: CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4.

P-gp-substrates: In vitro, sorafenib has been shown to inhibit the transport protein p-glycoprotein (P-gp). Increased plasma concentrations of P-gp substrates such as digoxin cannot be excluded with concomitant treatment with sorafenib.

Combination with other anti-neoplastic agents: In clinical studies Nexavar has been administered with a variety of other anti-neoplastic agents at their commonly used dosing regimens including gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with Nexavar resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolised by the UGT1A1 pathway, there was a 67 - 120% increase in the AUC of SN-38 and a 26 - 42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see section 4.4).
Docetaxel (75 or 100 mg/m^2 administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Days 2 through 19 of a 21-day cycle with a 3-day break in dosing around administration of docetaxel) resulted in a 36-80% increase in docetaxel AUC and a 16-32% increase in docetaxel C_{max}. Caution is recommended when sorafenib is co-administered with docetaxel (see section 4.4).

4.6 Pregnancy and lactation

There are no data on the use of sorafenib in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to cause harmful effects on the foetus. Nexavar should not be used during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and the risk to the foetus.
Women of childbearing potential must use effective contraception during treatment. Results from animal studies further indicate that sorafenib can impair male and female fertility (see section 5.3).

It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because sorafenib could harm infant growth and development (see section 5.3), women must not breast-feed during sorafenib treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. There is no evidence that Nexavar affects the ability to drive or to operate machinery.

4.8 Undesirable effects

The most common adverse reactions were diarrhoea, rash, alopecia and hand-foot syndrome (corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA).

Table 1: Adverse reactions reported in at least 5% of patients in any treatment group – study 11213 in renal cell carcinoma (see study 1 in section 5.1).

		Nexavar N=451			Placebo N=451		
System organ class	**Preferred term**	**all grades**	**grade 3**	**grade 4**	**all grades**	**grade 3**	**grade 4**
Metabolism and nutrition disorders	anorexia	9%	<1%	0%	5%	<1%	0%
Nervous system disorders	headache	6%	0%	0%	3%	0%	0%
Vascular disorders	hypertension	12%	2%	<1%	1%	<1%	0%
	flushing	6%	0%	0%	2%	0%	0%
Gastrointestinal disorders	diarrhoea	38%	2%	0%	9%	<1%	0%
	nausea	16%	<1%	0%	12%	<1%	0%
	vomiting	10%	<1%	0%	6%	<1%	0%

	constipation	6%	0%	0%	3%	0%	0%
Skin and subcutaneous tissue disorders	rash	28%	<1%	0%	9%	<1%	0%
	alopecia	25%	<1%	0%	3%	0%	0%
	hand foot syndrome**	19%	4%	0%	3%	0%	0%
	pruritus	17%	<1%	0%	4%	0%	0%
	erythema	15%	0%	0%	4%	0%	0%
	dry skin	11%	0%	0%	2%	0%	0%
	skin exfoliation	7%	<1%	0%	2%	0%	0%
Musculo-skeletal and connective tissue disorders	arthralgia	6%	<1%	0%	3%	0%	0%
	pain in extremity	6%	<1%	0%	2%	0%	0%
General disorders and administration site conditions	fatigue	15%	2%	0%	11%	<1%	0%
	asthenia	9%	<1%	0%	4%	<1%	0%

Table 2: Adverse reactions reported in at least 5% of patients in any treatment group – study 100554 in hepatocellular carcinoma (see study 3 in section 5.1).

		Nexavar N= 297			Placebo N= 302		
System organ class	**Preferred term**	**all grades**	**grade 3**	**grade 4**	**all grades**	**grade 3**	**grade 4**
Metabolism and nutrition disorders	anorexia	11%	<1%	0%	3%	<1%	0%
Gastrointestinal disorders	diarrhoea	39%	8%	0%	11%	2%	0%
	nausea	11%	<1%	0%	8%	1%	0%
	abdominal pain	7%	2%	0%	3%	<1%	0%
	vomiting	5%	1%	0%	3%	<1%	0%
Skin and subcutaneous tissue disorders	hand foot syndrome**	18%	7%	0%	2%	0%	0%
	alopecia	14%	0%	0%	2%	0%	0%
	rash	11%	<1%	0%	8%	0%	0%
	pruritus	8%	0%	0%	7%	<1%	0%
	dry skin	8%	0%	0%	4%	0%	0%
General disorders and administration site conditions	fatigue	17%	2%	<1%	13%	3%	<1%
	asthenia	6%	1%	<1%	2%	<1%	0%
Investigations	weight decreased	9%	2%	0%	<1%	0%	0%
Respiratory, thoracic and mediastinal disorders	hoarseness	5%	0%	0%	<1%	0%	0%

Adverse reactions reported in multiple clinical trials are listed below in Table 3, by system organ class (in MedDRA) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: All adverse reactions reported in patients in multiple clinical trials

System organ class	Very Common ≥ 1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100
Infections and infestations			folliculitis infection
Blood and lymphatic system disorders	lymphopenia	leucopenia neutropenia anaemia thrombocytopenia	
Immune system disorders			hypersensitivity reactions (including skin reactions and urticaria)
Endocrine disorders			hypothyroidism
Metabolism and nutrition disorders	hypophosphataemia	anorexia	hyponatraemia dehydration
Psychiatric disorders		depression	
Nervous system disorders		peripheral sensory neuropathy	reversible posterior leukoencephalopathy*
Ear and labyrinth disorders		tinnitus	
Cardiac disorders			myocardial ischaemia and infarction* congestive heart failure*
Vascular disorders	haemorrhage (inc. gastrointestinal*, respiratory tract* and cerebral haemorrhage*) hypertension		hypertensive crisis*
Respiratory, thoracic and mediastinal disorders		hoarseness	rhinorrhoea
Gastrointestinal disorders	diarrhoea nausea vomiting	constipation stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia	gastro oesophageal reflux disease pancreatitis gastritis gastrointestinal perforations*
Hepatobiliary disorders			increase in bilirubin and jaundice cholecystitis cholangitis
Skin and subcutaneous tissue disorders	rash alopecia hand foot syndrome** erythema pruritus	dry skin dermatitis exfoliative acne skin desquamation	eczema erythema multiforme minor keratoacanthoma/ squamous cell cancer of the skin

System organ class	Very Common ≥ 1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100
Musculoskeletal and connective tissue and disorders		arthralgia myalgia	
Renal and urinary disorders		renal failure	
Reproductive system and breast disorders		erectile dysfunction	gynaecomastia
General disorders and administration site conditions	fatigue pain (including mouth, abdominal, bone, tumour pain and headache)	asthenia fever influenza like illness	
Investigations	increased amylase increased lipase	weight decreased transient increase in transaminases	transient increase in blood alkaline phosphatase, INR abnormal, prothrombin level abnormal

* The adverse reactions may have a life-threatening or fatal outcome.
** hand foot syndrome corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA

Laboratory test abnormalities
Increased lipase and amylase were very commonly reported. CTCAE Grade 3 or 4 lipase elevations occurred in 11% and 9% of patients in the Nexavar group in study 1 (RCC) and study 3 (HCC), respectively, compared to 7% and 9% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% and 2% of patients in the Nexavar group in study 1 and study 3, respectively, compared to 3% of patients in each placebo group. Clinical pancreatitis was reported in 2 of 451 Nexavar treated patients (CTCAE Grade 4) in study 1, 1 of 297 Nexavar treated patients in study 3 (CTCAE Grade 2), and 1 of 451 patients (CTCAE Grade 2) in the placebo group in study 1.

Hypophosphataemia was a very common laboratory finding, observed in 45% and 35% of Nexavar treated patients compared to 12% and 11% of placebo patients in study 1 and study 3, respectively. CTCAE Grade 3 hypophosphataemia (1 – 2 mg/dl) in study 1 occurred in 13% of Nexavar treated patients and 3% of patients in the placebo group, in study 3 in 11% of Nexavar treated patients and 2% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphataemia (< 1 mg/dl) reported in either Nexavar or placebo patients in study 1, and 1 case in the placebo group in study 3. The aetiology of hypophosphataemia associated with Nexavar is not known.

CTCAE Grade 3 or 4 laboratory abnormalities occurring in ≥5% of Nexavar treated patients included lymphopenia and neutropenia.

4.9 Overdose

There is no specific treatment for Nexavar overdose. The highest dose of sorafenib studied clinically is 800 mg twice daily. The adverse events observed at this dose were primarily diarrhoea and dermatological events. In the event of suspected overdose Nexavar should be withheld and supportive care instituted where necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Protein kinase inhibitors, ATC code: L01XE05

Sorafenib is a multikinase inhibitor which has demonstrated both anti-proliferative and anti-angiogenic properties *in vitro* and *in vivo*.

Mechanism of action and pharmacodynamic effects
Sorafenib is a multikinase inhibitor that decreases tumour cell proliferation *in vitro*. Sorafenib inhibits tumour growth of a broad spectrum of human tumour xenografts in athymic mice accompanied by a reduction of tumour angiogenesis. Sorafenib inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, c-KIT, and FLT-3) and in the tumour vasculature (CRAF, VEGFR-2, VEGFR-3, and PDGFR-ß). RAF kinases are serine/threonine kinases, whereas c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-ß are receptor tyrosine kinases.

Clinical efficacy:
The clinical safety and efficacy of Nexavar have been studied in patients with hepatocellular carcinoma (HCC) and in patients with advanced renal cell carcinoma (RCC).

Hepatocellular carcinoma
Study 3 (study 100554) was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled study in 602 patients with hepatocellular carcinoma. Demographics and baseline disease characteristics were comparable between the Nexavar and the placebo group with regard to ECOG status (status 0: 54% vs. 54%; status 1: 38% vs. 39%; status 2: 8% vs. 7%), TNM stage (stage I: <1% vs. <1%; stage II: 10.4% vs. 8.3%; stage III: 37.8% vs. 43.6%; stage IV: 50.8% vs. 46.9%), and BCLC stage (stage B: 18.1% vs. 16.8%; stage C: 81.6% vs. 83.2%; stage D: <1% vs. 0%).

The study was stopped after a planned interim analysis of OS had crossed the prespecified efficacy boundary. This OS analysis showed a statistically significant advantage for Nexavar over placebo for OS (HR: 0.69, p= 0.00058, see Table 4). In the prespecified stratification factors (ECOG status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumour spread) the hazard ratio consistently favoured Nexavar over placebo. The descriptive subgroup analysis suggested a potentially less pronounced treatment effect for the subgroups of patients below 65 years of age and those with metastatic disease. There are limited data from this study in patients with Child Pugh B liver impairment and only one patient with Child Pugh C had been included.

Table 4: Efficacy Results from study 3 (study 100554) in hepatocellular carcinoma

Efficacy Parameter	Nexavar (N=299)	Placebo (N=303)	P-value	HR (95% CI)
Overall Survival (OS) [median, weeks (95% CI)]	46.3 (40.9, 57.9)	34.4 (29.4, 39.4)	0.00058*	0.69 (0.55, 0.87)
Time to Progression (TTP) [median, weeks (95% CI)]**	24.0 (18.0, 30.0)	12.3 (11.7, 17.1)	0.000007	0.58 (0.45, 0.74)

CI=Confidence interval, HR=Hazard ratio (Nexavar over placebo)
*statistically significant as the p-value was below the prespecified O'Brien Fleming stopping boundary of 0.0077
**independent radiological review

Renal cell carcinoma
The safety and efficacy of Nexavar in the treatment of advanced renal cell carcinoma (RCC) were investigated in two clinical studies:

Study 1 (study 11213) was a Phase III, multi-centre, randomised, double blind, placebo-controlled study in 903 patients. Only patients with clear cell renal carcinoma and low and intermediate risk MSKCC (Memorial Sloan Kettering Cancer Center) were included. The primary endpoints were overall survival and progression-free survival (PFS).
Approximately half of the patients had an ECOG performance status of 0, and half of the patients were in the low risk MSKCC prognostic group.
PFS was evaluated by blinded independent radiological review using RECIST criteria. The PFS analysis was conducted at 342 events in 769 patients. The median PFS was 167 days for patients randomised to Nexavar compared to 84 days for placebo patients (HR =0.44; 95% CI: 0.35-0.55; p<0.000001). Age, MSKCC prognostic group, ECOG PS and prior therapy did not affect the treatment effect size.

An interim analysis (second interim analysis) for overall survival was conducted at 367 deaths in 903 patients. The nominal alpha value for this analysis was 0.0094. The median survival was 19.3 months for patients randomised to Nexavar compared to 15.9 months for placebo patients (HR =0.77; 95% CI: 0.63-0.95; p=0.015). At the time of this analysis, about 200 patients had crossed-over to sorafenib from the placebo group.

Study 2 was a Phase II, discontinuation study in patients with metastatic malignancies, including RCC. Patients with stable disease on therapy with Nexavar were randomised to placebo or continued Nexavar therapy. Progression-free survival in patients with RCC was significantly longer in the Nexavar group (163 days) than in the placebo group (41 days) (p=0.0001, HR=0.29).

5.2 Pharmacokinetic properties

Absorption and distribution:
After administration of Nexavar tablets the mean relative bioavailability is 38 - 49% when compared to an oral solution. The absolute bioavailability is not known. Following oral administration sorafenib reaches peak plasma concentrations in approximately 3 hours. When given with a high-fat meal sorafenib absorption was reduced by 30% compared to administration in the fasted state.
Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered twice daily. *In vitro* binding of sorafenib to human plasma proteins is 99.5%.
Multiple dosing of Nexavar for 7 days resulted in a 2.5- to 7-fold accumulation compared to single dose administration. Steady state plasma sorafenib concentrations are achieved within 7 days, with a peak to trough ratio of mean concentrations of less than 2.

Metabolism and elimination:
The elimination half-life of sorafenib is approximately 25 - 48 hours. Sorafenib is metabolised primarily in the liver and undergoes oxidative metabolism, mediated by CYP 3A4, as well as glucuronidation mediated by UGT1A9.
Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows *in vitro* potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady state.

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in faeces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in faeces but not in urine, indicating that biliary excretion of unchanged drug might contribute to the elimination of sorafenib.

Pharmacokinetics in special populations: Analyses of demographic data suggest that there is no relationship between pharmacokinetics and age (up to 65 years) gender or body weight.

Paediatric Population: No studies have been conducted to investigate the pharmacokinetics of sorafenib in paediatric patients.

Race: There are no clinically relevant differences in pharmacokinetics between Caucasian and Asian subjects.

Renal impairment: In four Phase I clinical trials, steady state exposure to sorafenib was similar in patients with mild or moderate renal impairment compared to the exposures in patients with normal renal function. In a clinical pharmacology study (single dose of 400 mg sorafenib), no relationship was observed between sorafenib exposure and renal function in subjects with normal renal function, mild, moderate or severe renal impairment. No data is available in patients requiring dialysis.

Hepatic impairment: In hepatocellular carcinoma patients with mild or moderate hepatic impairment, exposure values were comparable and within the range of exposures observed in patients without hepatic impairment. There are no data for patients with Child-Pugh C (severe) hepatic impairment. Sorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

5.3 Preclinical safety data

The preclinical safety profile of sorafenib was assessed in mice, rats, dogs and rabbits.
Repeat-dose toxicity studies revealed changes (degenerations and regenerations) in various organs at exposures below the anticipated clinical exposure (based on AUC comparisons).
After repeated dosing to young and growing dogs effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate and alterations of the dentin composition. Similar effects were not induced in adult dogs.

The standard program of genotoxicity studies was conducted and positive results were obtained as an increase in structural chromosomal aberrations in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity in the presence of metabolic activation was seen. Sorafenib was not genotoxic in the Ames test or in the *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (< 0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test). Furthermore, the sorafenib batch tested in the standard genotoxicity battery included 0.34% PAPE.
Carcinogenicity studies have not been conducted with sorafenib.

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. An adverse effect on male and female fertility can however be expected because repeat-dose studies in animals have shown changes in male and female reproductive organs at exposures below the anticipated clinical exposure (based on AUC). Typical changes consisted of signs of degeneration and retardation in testes, epididymides, prostate, and seminal vesicles of rats. Female rats showed central necrosis of the corpora lutea and arrested follicular development in the ovaries. Dogs showed tubular degeneration in the testes and oligospermia.

Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below the clinical exposure. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased number of external and visceral malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
croscarmellose sodium
microcrystalline cellulose
hypromellose
sodium laurilsulfate
magnesium stearate

Coating:
hypromellose
macrogol (3350)
titanium dioxide (E 171)
ferric oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

112 (4 x 28) tablets in transparent (PP/Aluminium) blister packs.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer HealthCare AG
D-51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/06/342/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

July 2006

10. DATE OF REVISION OF THE TEXT

25 November 2008

10.2 Appendix 2: search strategy for section 6

10.2.1 - 10.2.3 Databases searched, search dates & datespan of search

Service Provider: Dialog DataStar

1. Medline (Dialog Datastar 1950 to 21st November 2008)
2. EMBASE (Dialog Datastar 1974 to 21st November 2008)

Cochrane Library 2008 Issue 4 including (to December 2008):

3. The Cochrane Database of Systematic Reviews (Cochrane Reviews)
4. Database of Abstracts of Reviews of Effects (DARE)
5. The Cochrane Central Register of Controlled Trials (CENTRAL)
6. The Cochrane Database of Methodology Reviews (Methodology Reviews / Register)
7. Health Technology Assessment Database (HTA)
8. NHS Economic Evaluation Database (NHS EED)
9. Cochrane Groups

In addition, the following internet resources & conference proceedings were searched:

- American Society of Clinical Oncology (ASCO) (http://www.asco.org)
- European Cancer Conference (ECCO)
- http://www.clinicaltrials.gov

10.2.4 Search Strategies

Medline (Dialog Datastar) (MEZZ)
1950 to 21st November 2008
No date limits were applied

The search was carried out on 21st November 2008.

Strategy for sorafenib
This search retrieved 19 references

1. exp Liver Neoplasms/ (99091)
2. HCC.TI,AB. (15191)
3. (hepatic or hepatocellular or liver).TI,AB. (593570)
4. (cancer or carcinoma).TI,AB. (940638)
5. 3 and 4 (72383)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (75778)
7. (advanced or unresectable or inoperable).TI,AB. (187018)
8. 6 and 7 (6916)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (962332)
10. 8 not 9 (3758)
11. exp Drug Therapy/ (427928)
12. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (1284003)
13. 11 or 12 AND LG=EN AND HUMANS =YES (954158)
14. 10 and 13 (1839)
15. (sorafenib or nexavar or sorafinib).TI,AB. AND LG=EN AND HUMAN=YES (368)
16. 14 and 15 (19)

Strategy for doxorubicin
This search retrieved 221 references

1. exp Liver Neoplasms/ (99091)
2. HCC.TI,AB. (15191)
3. (hepatic or hepatocellular or liver).TI,AB. (593570)
4. (cancer or carcinoma).TI,AB. (940638)
5. 3 and 4 (72383)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (75778)
7. (advanced or unresectable or inoperable).TI,AB. (187018)
8. 6 and 7 (6916)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (962332)
10. 8 not 9 (3758)
11. exp Drug Therapy/ (427928)
12. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (1284003)

13. 11 or 12 AND LG=EN AND HUMANS =YES (954158)
14. 10 and 13 (1839)
15. (doxorubicin or doxyrubicin or adriamycin).TI,AB. AND LG=EN AND HUMAN=YES (19438)
16. 14 and 15 (221)

Strategy for placebo / best supportive care
This search retrieved 43 references

1. exp Liver Neoplasms/ (99091)
2. HCC.TI,AB. (15191)
3. (hepatic or hepatocellular or liver).TI,AB. (593570)
4. (cancer or carcinoma).TI,AB. (940638)
5. 3 and 4 (72383)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (75778)
7. (advanced or unresectable or inoperable).TI,AB. (187018)
8. 6 and 7 (6916)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (962332)
10. 8 not 9 (3758)
11. exp Drug Therapy/ (427928)
12. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (1284003)
13. 11 or 12 AND LG=EN AND HUMANS =YES (954158)
14. 10 and 13 (1839)
15. (placebo or supportive or BSC or (best adj supportive)).TI,AB. (149056)
16. 14 and 15 (43)

Strategy for natural history of advanced HCC
This search retrieved 0 references

1. exp Liver Neoplasms/ (99091)
2. HCC.TI,AB. (15191)
3. (hepatic or hepatocellular or liver).TI,AB. (593570)
4. (cancer or carcinoma).TI,AB. (940638)
5. 3 and 4 (72383)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (75778)
7. (advanced or unresectable or inoperable).TI,AB. (187018)
8. 6 and 7 (6916)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (962332)
10. 8 not 9 (3758)
11. exp Natural history/ (301)
12. 10 and 11 (0)

EMBASE (EMZZ) (Dialog Datastar)
1974 to 21st November 2008

The search was conducted on 21st November 2008.

Strategy for sorafenib
This search retrieved 33 references

1. exp Liver Cancer/ (66644)
2. HCC.TI,AB. (12172)
3. (hepatic or hepatocellular or liver).TI,AB. (412038)
4. (cancer or carcinoma).TI,AB. (696014)
5. 3 and 4 (56696)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (57878)
7. (advanced or unresectable or inoperable).TI,AB. (145051)
8. 6 and 7 (6472)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (714112)
10. 8 not 9 (3532)
11. exp Drug Therapy/ (848185)
12. exp Antineoplastic Agent/ (716689)
13. exp Systemic Therapy/ (1708)
14. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (998562)
15. 11 or 12 or 13 or 14 AND LG=EN AND HUMAN=YES (1160080)
16. 10 and 15 (2310)
17. sorafenib or sorafinib or nexavar AND LG=EN AND HUMAN=YES (349)
18. 16 and 17 (33)

Strategy for doxorubicin
This search retrieved 594 references

1. exp Liver Cancer/ (66644)
2. HCC.TI,AB. (12172)
3. (hepatic or hepatocellular or liver).TI,AB. (412038)
4. (cancer or carcinoma).TI,AB. (696014)
5. 3 and 4 (56696)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (57878)
7. (advanced or unresectable or inoperable).TI,AB. (145051)
8. 6 and 7 (6472)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (714112)
10. 8 not 9 (3532)
11. exp Drug Therapy/ (848185)
12. exp Antineoplastic Agent/ (716689)
13. exp Systemic Therapy/ (1708)
14. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (998562)
15. 11 or 12 or 13 or 14 AND LG=EN AND HUMAN=YES (1160080)
16. 10 and 15 (2310)
17. (doxorubicin or doxyrubicin or adriamycin).TI,AB. AND LG=EN AND HUMAN=YES (16677)
18. exp doxorubicin/ (82847)
19. 17 or 18 (58156)
20. 16 and 19 (594)

Strategy for placebo / best supportive care

This search retrieved 71 references

1. exp Liver Cancer/ (66644)
2. HCC.TI,AB. (12172)
3. (hepatic or hepatocellular or liver).TI,AB. (412038)
4. (cancer or carcinoma).TI,AB. (696014)
5. 3 and 4 (56696)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (57878)
7. (advanced or unresectable or inoperable).TI,AB. (145051)
8. 6 and 7 (6472)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (714112)
10. 8 not 9 (3532)
11. exp Drug Therapy/ (848185)
12. exp Antineoplastic Agent/ (716689)
13. exp Systemic Therapy/ (1708)
14. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (998562)
15. 11 or 12 or 13 or 14 AND LG=EN AND HUMAN=YES (1160080)
16. 10 and 15 (2310)
17. (placebo or supportive or BSC or (best adj supportive).TI,AB. (127743)
18. 10 and 11 (71)

Strategy for natural history of advanced HCC

This search retrieved 34 references

1. exp Liver Cancer/ (66644)
2. HCC.TI,AB. (12172)
3. (hepatic or hepatocellular or liver).TI,AB. (412038)
4. (cancer or carcinoma).TI,AB. (696014)
5. 3 and 4 (56696)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (57878)
7. (advanced or unresectable or inoperable).TI,AB. (145051)
8. 6 and 7 (6472)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (714112)
10. 8 not 9 (3532)
11. exp History/ (34591)
12. (natural and history).TI,AB. (25293)
13. 11 or 12 (58755)
14. 10 and 13 AND LG=EN AND HUMAN=YES (34)

Cochrane Library 2008 Issue 4 including:

The Cochrane Database of Systematic Reviews (Cochrane Reviews)
Database of Abstracts of Reviews of Effects (DARE)
The Cochrane Central Register of Controlled Trials (CENTRAL)
The Cochrane Database of Methodology Reviews / Register (Methodology Reviews / Register)
Health Technology Assessment Database (HTA)
NHS Economic Evaluation Database (NHS EED)
Cochrane Groups

The search was conducted on 11th November 2008.
Strategy for sorafenib, doxorubicin and placebo / best supportive care

[NB This search allowed for collection of references for the clinical and cost effectiveness sections of the analysis.]

This search retrieved 1 reference for sorafenib, 144 for doxorubicin, 99 for placebo / best supportive care and 11 references for natural history

#1 (hepatocellular):ti,ab,kw or (hepatic):ti,ab,kw or (liver):ti,ab,kw
#2 (cancer):ti,ab,kw or (carcinoma):ti,ab,kw
#3 (#1 AND #2)
#4 (#3 AND (advanced OR inoperable OR unresectable))
#5 (#4 AND (sorafenib OR nexavar))
#6 (#4 AND (doxorubicin OR adriamycin))
#7 (#4 AND (placebo OR supportive))
#8 (#4 AND (natural AND history))

American Society of Clinical Oncology (ASCO) (Internet http://www.asco.org)
2000 – 2008

The search was conducted on 11th November 2008 and produced 96 references.

Due to the limits of the search database, searching was done by year and then collated.

- (hepatocellular or hepatic or liver) in the title AND
- (sorafenib or placebo or nexavar or supportive or doxorubicin or adriamycin) in the abstract body (90 references)

- (hepatocellular or hepatic or liver) in the title AND
- (natural and history) in the abstract body (6 abstracts)

European Cancer Conference (ECCO)

The search was conducted on 11th November 2008 and produced 2 references.
This search covered both clinical and cost-effectiveness abstracts.

Due to the limits of the search database and to the abstracts available online, searching was done by year and then collated.

Search terms: hepatocellular or hepatic or liver

ECCO 14 (2007) – 1 abstract
ECCO 13 (2005) – 1 abstract
ECCO 12 (2003 – 0 abstracts

10.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

No additional searches of company databases were carried out.

10.2.6 The inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Patient Group	Patients; Patients of 18 years and over with a diagnosis of advanced inoperable HCC	Patients; No prior *systemic* therapy (as this was one of the inclusion criteria for the phase III SHARP trial)
Intervention	Phase III studies. Single or Double blind RCT. Phase II. Studies with sorafenib (as a single-agent), placebo, doxorubicin (Adriamycin) or best supportive care as a treatment arm.	Phase I studies. Studies reporting data on secondary liver cancer e.g. colorectal cancer with liver metastases. Transarterial embolisation (TAE) and Transarterial Chemo-embolisation (TACE) studies were excluded. Trials of intra-arterial agents were excluded.
Outcomes	All patient outcomes were considered in the search, however we focused on gathering data on the following outcomes: Overall Survival, Time to progression, Progression-free survival, Response rate (including complete and partial	

	Inclusion criteria	Exclusion criteria
	response), Adverse events of treatment, Health-related quality of life Costs from all reported perspectives	

Only English language papers were included. Studies reported in abstract form only with no further information available online or via Bayer were excluded.

10.2.7 The data abstraction strategy

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the inclusion / exclusion criteria set out above. Studies that did not meet all the criteria were excluded. Data was extracted by one reviewer and was checked by a second reviewer. Any discrepancies were resolved by consensus. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Where available the following data were reviewed: Baseline characteristics, Overall Survival, Time to progression, Progression-free survival, Response rate (including complete and partial response), Adverse events, Health-related quality of life, costs from all reported perspectives.

10.3 Appendix 3: search strategy for section 7

10.3.1 – 10.3.3 Databases searched, Date & Datespan of search

The following databases were used for identification of economic papers to April 2008.

Service Provider: Dialog DataStar

1. Medline (MEDL) (Dialog Datastar)
2. Excerpta Medica (EMED) (Dialog Datastar)

Cochrane Library 2008 Issue 1 including (to April 2008):

3. The Cochrane Database of Systematic Reviews (Cochrane Reviews)
4. Database of Abstracts of Reviews of Effects (DARE)
5. The Cochrane Central Register of Controlled Trials (CENTRAL)
6. The Cochrane Database of Methodology Reviews (Methodology Reviews / Register)
7. Health Technology Assessment Database (HTA)
8. NHS Economic Evaluation Database (NHS EED)
9. Cochrane Groups
10. OHE Health Economic Evaluation Database (HEED) (cost-effectiveness evidence only; to December 2008)

10.3.4 Search strategies for cost-effectiveness studies

Medline (Dialog Datastar) (MEZZ)
1950 to 5th December 2008
No date limits were applied

1. exp Liver Neoplasms/ (99091)
2. HCC.TI,AB. (15191)
3. (hepatic or hepatocellular or liver).TI,AB. (593570)
4. (cancer or carcinoma).TI,AB. (940638)
5. 3 and 4 (72383)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (75778)
7. (advanced or unresectable or inoperable).TI,AB. (187018)
8. 6 and 7 (6916)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (962332)
10. 8 not 9 (3758)
11. exp Drug Therapy/ (427928)
12. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (1284003)
13. 11 or 12 AND LG=EN AND HUMANS =YES (954158)
14. 10 and 13 (1839)
15. exp Health Care Economics and Organizations/ (987746)
16. exp Economics/ (406979)
17. exp “Costs and Cost analysis”/ (142823)
18. exp “Quality-of-Life”/ (73208)
19. exp “Quality-of-Health-Care”/ (3520215)
20. healthcare or health adj care.ti,ab. (209671)
21. health adj (gain or related or measurement or state).ti,ab. (150202)
22. wellbeing.ti,ab. (2590)
23. economic$ or pharmacoeconomic$ (181835)
24. cost or costs or costly or costed or costing.ti,ab. (222024)
25. utility or utilities or benefit$ (376190)
26. price or prices or pricing (34175)
27. quality and life (135471)
28. QALY or QUALY or QALYS or QUALYS or (quality adj adjusted adj life adj year$) (5375)
29. cost adj effectiveness (23205)
30. exp Quality-Adjusted-Life-Years/. (3732)
31. treatment with outcome (400285)
32. outcome adj assessment (33154)
33. euroqol or euro adj qol or euroqual or eur adj qual or eq-5d or eq5d or eq adj 5d (1724)
34. eortc adj qlq-c30 or qlq-c30 or hrqol or hrql or hql or qol (15852)
35. HYE or (health adj year adj equivalent) (93)
36. Fact-hep or facthep or fact adj hep (12)
37. fhsi-8 or fhsi8 or fhsi (8)
38. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 AND LG=EN AND HUMAN=YES (4227790)

39. 14 and 38 (1097)

EMBASE (EMZZ) (Dialog Datastar)
1974 to 8th December 2008

The search was carried out on 8th December 2008

1. exp Liver Cancer/ (66644)
2. HCC.TI,AB. (12172)
3. (hepatic or hepatocellular or liver).TI,AB. (412038)
4. (cancer or carcinoma).TI,AB. (696014)
5. 3 and 4 (56696)
6. 1 or 2 or 5 AND LG=EN AND HUMAN=YES (57878)
7. (advanced or unresectable or inoperable).TI,AB. (145051)
8. 6 and 7 (6472)
9. (breast or lung or colorectal or colon or gastric or ovarian or pancreatic).TI,AB. (714112)
10. 8 not 9 (3532)
11. exp Drug Therapy/ (848185)
12. exp Antineoplastic Agent/ (716689)
13. exp Systemic Therapy/ (1708)
14. (systemic or therapy or chemotherapy or salvage or anticancer or antineoplastic).TI,AB. (998562)
15. 11 or 12 or 13 or 14 AND LG=EN AND HUMAN=YES (1160080)
16. 10 and 15 (2310)
17. exp Health-Economics/ (226893)
18. exp Economic-Aspect/ (378556)
19. exp Cost-Benefit-Analysis/ (29680)
20. exp Quality-of-Life/ (97343)
21. Quality-Adjusted-Life-Year#.DE. or Health-Care-Quality#.DE. or Quality-of-Life-Index#.DE. (764748)
22. healthcare or health adj care (429526)
23. health and (gain or related or measurement or state) (295697)
24. wellbeing (17666)
25. economic$ or pharmacoeconomic$ (150136)
26. cost or costs or costly or costed or costing (257782)
27. utility or utilities or benefit$ (293772)
28. price or prices or pricing (23522)
29. quality and life (107059)
30. QALY or QUALY or QALYS or QUALYS or quality adj adjusted adj life adj year$ (5071)
31. cost adj effectiveness (61227)
32. treatment with outcome (343764)
33. outcome with assessment (103669)
34. euroqol or euro adj qol or euroqual or eur adj qual or eq-5d or eq5d or eq adj 5d (883)
35. eortc adj qlq-c30 or qlq-c30 or hrqol or hrql or hql or qol (12627)
36. HYE or (health adj year adj equivalent) (453)
37. Fact-hep or facthep or fact adj hep (9)
38. fhsi-8 or fhsi8 or fhsi (5)
39. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 AND LG=EN AND HUMAN=YES (not recorded)
40. 16 and 39 (1196)

Cochrane Library – see clinical search section 9.2.4

American Society of Clinical Oncology (Internet http://www.asco.org)
2000 – 2008

The search was conducted on 11th November 2008 and produced 164 references.

- (hepatocellular or hepatic or liver) in the title AND
- (natural and history) in the abstract body (6 abstracts)

- (hepatocellular or hepatic or liver) in the title AND
- gain or state or wellbeing or economic or economics or pharmacoeconomic$ or cost$ or quality or QALY (23 abstracts)

- (hepatocellular or hepatic or liver) in the title AND
- QUALY or pric$ or benefit or utility or effectiveness or FACT-HEP or FHSI-8 (135 abstracts)

- (hepatocellular or hepatic or liver) in the title AND
- euroqol or eq-5d or eq5d or eq 5d or euro qol or QLQ-C30 OR HRQOL OR HRQL OR HQL OR QOL (0 abstracts)

European Cancer Conference (ECCO)

See clinical search strategy

Office of Health Economics Health Economic Evaluation Database (OHE HEED)

Search carried out on 9th December 2008
Hepatic or Liver or Hepatocellular AND Cancer or carcinoma (226 hits)

10.3.5 Additional searches

No additional searches were carried out.

10.3.6 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Patient Group	Patients; Patients with a diagnosis of advanced inoperable HCC	
Intervention	Phase III studies. Single or Double blind RCT. Phase II. All systemic anticancer therapy	Transarterial embolisation (TAE) and Transarterial Chemo-embolisation (TACE) studies were excluded.
Outcomes	Health-related quality of life Costs from all reported perspectives	

10.4 Appendix 4: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

10.5 Appendix 5:Definition and criteria of Child-Pugh classification

Measure	Score		
	1 point	**2 points**	**3 points**
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL) **(µmol/L)**	<2.0 <34	2.0-3.0 34-50	>3.0 >50
Albumin (g/dL) **(g/L)**	>3.5 >35	2.8-3.5 28-35	<2.8 <28
PT prolonged (sec) **PT prolonged (%)** **INR**	<4 >60 <1.7	4-6 40-60 1.7-2.3	>6 <40 >2.3
Encephalopathy	Stage 0-Absent	Stage 1-2 – Moderate	Stage 3-4 - Severe

Child-Pugh A: 5 or 6 points

Child-Pugh B: 7-9 points

Child-Pugh C: >9 points

10.6 Appendix 6: Summary of Response Evaluation Criteria in Solid Tumours (RECIST)

Complete response (CR)	Disappearance of all clinical and radiological evidence of tumour
Partial response (PR)	At least a 30% decrease in the sum of longest diameter (LD) of target lesions taking as reference the baseline sum LD
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD
Progressive disease (PD)	At least a 20% increase in the sum of LD of measured lesions taking as reference the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions

10.7 Appendix 7: FHSI-I

FACT Hepatobiliary Symptom Index
FHSI-I

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
HI 7	I feel fatigued	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

10.8 Appendix 8: FACT-Hep

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

10.9 Appendix 9: WHO modified criteria for tumour response

Objective response:

Complete response (CR)	Disappearance of all known lesion(s); confirmed at 4 weeks
Partial response (PR)	At least 50% decrease; confirmed at 4 weeks
Stable disease (SD)	Neither PR nor PD criteria met
Progressive disease (PD)	An increase of 25% or more in the sum of all target lesions area; no CR, PR or SD documented before increased disease

10.10 Appendix 10: Extrapolation of clinical trial data

Fit of distributions

AIC (Akaike information criteria) shows that a lognormal model provides a significantly better fit than a Weibull, a loglogistic, an exponential, or a Gompertz distribution in the sorafenib group, and as good as the loglogistic distribution in the placebo group.

Table 1: Time to death, Sorafenib group

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Time to death, Placebo group

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Time to progression, Sorafenib group

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Time to progression, Placebo group

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TTP and OS Lognormal parameters

Table 1 Lognormal parameters

	TTP		OS	
	Mu	**Sigma**	**Mu**	**Sigma**
Total population (base case)				
Sorafenib	4.822	0.983	5.791	1.147
BSC	4.513	0.804	5.465	1.019
TNM Stage I-III				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis C from lab				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
No extra hepatic spread				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
No tumour burden				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Age =>65				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Without macrovascular invasion				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
With macrovascular invasion				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
BCLC stage B				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
BCLC stage C				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Child Pugh A				
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 Variance covariance matrices

		TTP		OS	
		const	ln sigma	const	ln sigma
Total population (base case)					
Sorafenib	const	0.004267	-	0.007019	-
	ln sigma	0.000836	0.002994	0.002415	0.004141
BSC	const	0.002534	-	0.00449	-
	ln sigma	0.000283	0.002373	0.001211	0.003221
TNM Stage I-III					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis C from lab					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
No extrahepatic spread					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
No tumour burden					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
Age =>65					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
Without macrovascular invasion					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
With macrovascular invasion					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]

		TTP		OS	
BCLC stage B					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BCLC stage C					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
Child Pugh A					
Sorafenib	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]
BSC	const	[redacted]	[redacted]	[redacted]	[redacted]
	ln sigma	[redacted]	[redacted]	[redacted]	[redacted]

10.11 Appendix 11: Systematic review of the utility literature

To ensure that all relevant studies were identified, a systematic review of the published literature was conducted. Three approaches were used to search for relevant data.

1. A search of published literature using the electronic database EMBASE.com which includes EMBASE and Medline

2. Retrieval of primary references for utility weights cited by authors of papers retrieved in approach 1 above

3. Retrieval of primary references for utility weights cited in relevant HTA reports and other systematic reviews.

The overall aim of the search was to identify published papers that described preference-based utility weights for progressive HCC and stable disease. A summary of the literature search strategies that were employed is presented in **Table 1**. Medline and EMBASE were searched concurrently using EMBASE.com. The search was limited to papers published after 1972, as utility theory seldom related to the health care setting prior to that date. Duplicate citations were removed and all relevant papers retrieved. The first search was performed in January 3rd 2008, this search was updated on November 19th 2008. The results incorporate the results from both searches.

Table 1: Search strategy for health-related quality of life (utility) values in HCC (first search Jan 3rd 2008)

Search location	Search strategy	Citations retrieved	Total citations
EMBASE.com *(searched 03 Jan 2008)*	#1: 'liver cell carcinoma'/syn [a]	64,856	26
	#2: ((‘cost utility analysis’/exp OR ‘cost utility analysis’) OR (‘cost utility’/exp OR ‘cost utility’) OR (‘standard gamble’) OR (‘time trade-off’) OR (‘time trade-off’) OR (‘qaly’/exp OR ‘qaly’) OR (‘quality adjusted life years’/exp OR ‘quality adjusted life years’) OR (‘preference weights’) OR (‘preference based health related quality of life’) OR (‘preference based hrqol’) OR (‘cost utilities’) OR (‘utility weight’) OR (‘utility weights’) OR (‘quality adjusted life year’/exp OR ‘quality adjusted life year’) OR (‘utility value’) OR (‘utility values’)) OR (‘multiattribute utility’) OR (((tto) NOT (‘tobacco retrotransposon’)) NOT (‘tea tree oil’/exp OR ‘tea tree oil’)) OR (‘health utilities’) OR (‘health utility’) OR (sf6d) OR (‘assessment of quality of life instrument’) OR (‘euroqol’) OR (eq5d) OR (‘short form 6d’) OR (‘hui 3’) OR (‘hui iii’)	9,456	
	#3: #1 AND #2	26	

[a] The EMBASE.com synonyms list for ‘liver cell carcinoma’ includes: carcinoma, hepatocellular; carcinoma, hepatic cell; carcinoma, liver cell; hepatic cell carcinoma; hepatocarcinoma; hepatocellular carcinoma; hepatoma; malignant hepatoma

All citations identified in the searches described in **Table 1** were reviewed. This was initially performed using the publication title and, where available, the abstract. Publications were excluded for the following reasons:

1) Wrong publication type: narrative review, opinion piece, note
2) Wrong indication: not HCC
3) No preference-based utility weights reported

Table 2: Summary of identification of health-related quality of life in patients with HCC from the search of the published literature (first search Jan 3rd 2008)

	EMBASE and Medline
Number of citations retrieved	26
Number of citations excluded after title/abstract review - Wrong publication type - Wrong indication - No preference-based utility weights reported TOTAL	 5 2 0 7
Number of publications that were reviewed using full text	19
Number of citations excluded after title/abstract review - Wrong publication type - Wrong indication - No preference-based utility weights reported TOTAL	 1 0 3 4
Number of included citations	15
Number of additional citations identified by manual searching of references	7
Number of included studies reporting utility weights (primary and secondary studies)	22

The Embase and Medline search resulted in 15 papers that could be included. Another seven were identified by manual searching of references. So a total of 22 publications that report utility weights for HCC were included from the first search performed in January 2008. The citation details of these 22 publications are provided below in Table 5. Citation details of excluded studies complete with their reason for exclusion is presented in the Appendix.

The updated search yielded 39 citations, shown in **Table 3.**

Table 3: Search strategy and results for health-related quality of life (utility) values in HCC (updated search Nov 19th 2008)

Search location	Search strategy	Citations retrieved	Total citations
EMBASE.com *(searched 19 Nov 2008)*	#1: 'liver cell carcinoma'/syn [a]	69,033	39
	#2: ((‘cost utility analysis’/exp OR ‘cost utility analysis’) OR (‘cost utility’/exp OR ‘cost utility’) OR (‘standard gamble’) OR (‘time trade-off’) OR (‘time trade-off’) OR (‘qaly’/exp OR ‘qaly’) OR (‘quality adjusted life years’/exp OR ‘quality adjusted life years’) OR (‘preference weights’) OR (‘preference based health related quality of life’) OR (‘preference based hrqol’) OR (‘cost utilities’) OR (‘utility weight’) OR (‘utility weights’) OR (‘quality adjusted life year’/exp OR ‘quality adjusted life year’) OR (‘utility value’) OR (‘utility values’)) OR (‘multiattribute utility’) OR (((tto) NOT (‘tobacco retrotransposon’)) NOT (‘tea tree oil’/exp OR ‘tea tree oil’)) OR (‘health utilities’) OR (‘health utility’) OR (sf6d) OR (aqol) OR (‘australian quality of life’) OR (‘assessment of quality of life instrument’) OR (‘euroqol’) OR (eq5d) OR (‘short form 6d’) OR (‘hui 3’) OR (‘hui iii’)	10,777	
	#3: #1 AND #2	39	

[a] The EMBASE.com synonyms list for ‘liver cell carcinoma’ includes: carcinoma, hepatocellular; carcinoma, hepatic cell; carcinoma, liver cell; hepatic cell carcinoma; hepatocarcinoma; hepatocellular carcinoma; hepatoma; malignant hepatoma

All citations identified in the searches described in **Table 3** were reviewed. This was initially performed using the publication title and, where available, the abstract. Publications were excluded for the following reasons:

1) Wrong publication type: narrative review, opinion piece, note
2) Wrong indication: not HCC
3) No preference-based utility weights reported

4) Citation had previously been included in literature review conducted with Bayer on 3rd January 2008.

Table 4: Summary of identification of health-related quality of life in patients with HCC from the search of the published literature (updated search Nov 19th 2008)

	EMBASE and Medline
Number of citations retrieved	39
Number of citations excluded after title/abstract review - Wrong publication type - Wrong indication - No preference-based utility weights reported - Previously identified in literature review of 3rd January 2008 TOTAL	 0 0 0 26 26
Number of publications that were reviewed using full text	13
Number of citations excluded after title/abstract review - Wrong publication type - Wrong indication - No preference-based utility weights reported TOTAL	 1 1 2 4
Number of included citations	9
Number of additional citations identified by manual searching of references (not previously identified in literature review of 3rd January 2008)	3
Number of included studies reporting utility weights (primary and secondary studies)	12

As summarised in **Table 4** the application of the exclusion criteria identified thirteen potentially relevant publications in the updated search. Full publications were retrieved and the exclusion criteria applied again. Four publications were excluded after reviewing the full text as they did not report preference-based utility weights or were in the wrong indication (You et al 2008, Singal et al 2008, Dan et al 2008 and McLernon et al 2008). Nine citations were identified that had not previously been included in the literature review conducted in January 2008 and were otherwise eligible for inclusion (Coon et al. 2007; Coon et al. 2008; Levy et al.2008; Nouso et al. 2008;Veenstra et al. 2008a; Veenstra et al. 2008b; Yuan et al. 2008a; and Yuan et al. 2008b, Siew et al 2008). Two of these studies reported primary utility data (Levy et al. 2008, Siew et al 2008).

From hand searching the reference list of the included articles we identified three studies that reported utility data for HCC and had not previously been included in the literature review in January 2008 (Siebert et al. 2003 cited in McLernon et al. 2008, Kanwal et al 2005 in Yuan et al 2008a and Salomon et al 2003 in Nouso et al 2008).

The citation details of these twelve publications are provided below in **Table 5**.

Table 5: Included publications reporting utility weights for HCC

#	Citation	From updated search
1	Arguedas MR, Chen VK, Eloubeidi MA, and Fallon MB. (2003) Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: A cost-utility analysis. *American Journal of Gastroenterology* 98:679-690.	No
2	Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, and Davis GL. (1997) Estimates of the cost-effectiveness of a single course of interferon-alpha2B in patients with histologically mild chronic hepatitis C. *Annals of Internal Medicine* 127:855-865.	No

3	Buti M, Casado MA, Fosbrook L, Wong JB, and Esteban R. (2000) Cost-effectiveness of combination therapy for naı¨ve patients with chronic hepatitis C. *Journal of Hepatology* 33:651-658.	No
4	Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, and Stein K. (2006) The cost-effectiveness of testing for hepatitis C in former injecting drug users. *Health technology assessment* (Winchester, England) 10:iii-xii, 1.	No
5	Chong CAKY, Gulamhussein A, Healthcote J, Lilly L, Sherman M, Naglie G, Krahn M. (2003) Health-state utilities and quality of life in hepatitis C patients. *American Journal of Gastroenterology* 98:630-638.	No
6	Coon JT, Rogers Gm Hewson P et al. (2007) Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health technology Assessment* 11(34)	Yes
7	Coon JT, Rogers G, Hweston P et al. (2008) Surveillance of cirrhosis for hepatocellular carcinomaL a cost-utility analysis. *British Journal fo Cancer* 98: 1166-1175	Yes
8	Crowley SJ, Tognarini D, Desmond PV, and Lees M. (2000) Cost-effectiveness analysis of lamivudine for the treatment of chronic hepatitis B. *PharmacoEconomics* 17:409-427.	No
9	Del Rio RA, Post AB, and Singer ME. (2006) Cost-effectiveness of hematologic growth factors for anemia occuring during hepatitis C combination therapy. *Hepatology* 44:1598-1606.	No
10	Enriquez AD, Campbell MS, and Reddy KR. (2007) Cost-effectiveness of suppressing hepatitis B virus DNA in immune tolerant patients to prevent hepatocellular carcinoma and cirrhosis. *Alimentary Pharmacology and Therapeutics* 26:383-391.	No
11	Kanwal F, Gralnek IM, Martin P, et al. Treatment alternatives for chronic hepatitis B virus infection: a cost-effectiveness analysis. *Ann Intern Med* 2005; 142:821–31.	Yes
12	Law MG, Dore GJ, Bath N, Thompson S, Crofts N, Dolan K, Giles W, Gow P, Kaldor J, Loveday S, Powell E, Spencer J, and Wodak A. (2003) Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001. *International Journal of Epidemiology* 32:717-724.	No
13	Levy AR, Kowdley KV, Iioeje U et al. (2008) The impact of chronic hepatitis B on Quality of Life: A multinational study of utilities from infected and uninfected persons. *Value in health*11(3): 527-538	Yes
14	Lin OS, Keeffe EB, Sanders GD, and Owens DK. (2004) Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. *Alimentary Pharmacology and Therapeutics* 19:1159-1172.	No
15	Nouso K, Tanaka H, Uematsu S et al. (2008) Cost-effectiveness of the surveillance program of hepatocellular carcinoma depends on the medial circumstances. *Journal of Gastroenterology and Hepatology* 23: 437-444	Yes
16	Patel D, Terrault NA, Yao FY, Bass NM, and Ladabaum U. (2005) Cost-effectiveness of hepatocellular carcinoma surveillance in patients with hepatitis C virus-related cirrhosis. *Clinical Gastroenterology and Hepatology* 3:75-84.	No
17	Pwu RF, and Chan KA. (2002) Cost-effectiveness analysis of interferon-a therapy in the treatment of chronic hepatitis B in Taiwan. *Journal of Formosan Medical Association* 101:632-641.	No
18	Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA 2003; 290: 228–37.	Yes
19	Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, and Hadengue A. (2001) Living donor liver transplantation for early hepatocellular carcinoma: A life-expectancy and cost-effectiveness perspective. *Hepatology* 33:1073-1079.	No
20	Shepherd J, Jones J, Takeda A, Davidson P, and Price A. (2006) Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: A systematic review and economic evaluation. *Health Technology Assessment* 10:1-122.	No
21	Shiell A, Brown S, Farrell GC. (1999) Hepatitis C: an economic evaluation of extended treatment with interferon. *Medical Journal of Australia* 171:189-193.	No
22	Siebert U, Sroczynski G, Rossol S et al.(2003) Cost effectiveness of peginterferon α-2b plus ribavirin versus interferon α-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut*: 52:425–432	Yes
23	Siew, C. O., B. Mak, et al. (2008). "Health-related quality of life in chronic hepatitis B patients." *Hepatology* **47**(4): 1108-1117	Yes
24	Singer ME, Younossi ZM. (2001) Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. *American Journal of Medicine* 111:614–621.	No
25	Sinha M and Das A. (2000) Cost effectiveness analysis of different strategies of management of chronic hepatitis C infection in children. *Pediatric Infectious Disease Journal* 19:23-30.	No
26	Veenstra DL, Spackman DE, Biscegile A et al. (2008a) Evaluating anti-viral drug selection and treatment duration in HBeAg-negative chronic hepatitis B: a cost-effectiveness analysis. *Alimentary Pharmacology & Therapeutics* 27: 1240-1252	Yes

27	Veenstra DL, Sullivan SD, Lai MY (2008) HBeAg-Negative chronic hepatitis B: Cost-effectiveness of peginterferon alfa-2a compared to lamivudine in Taiwan.*Value in Health*11(2): 131-138	Yes
28	Wells CD, Murrill WB, and Arguedas MR. (2004) Comparison of health-related quality of life preferences between physicians and cirrhotic patients: Implications for cost-utility analyses in chronic liver disease. *Digestive Diseases and Sciences* 49:453-458.	No
29	Wong JB, Koff RS, Tine F, and Pauker SG. (1995) Cost-effectiveness of interferon-(alpha)2b treatment for hepatitis B e antigen- positive chronic hepatitis B. *Annals of Internal Medicine* 122:664-675.	No
30	Wong JB, Bennett WG, Koff RS, and Pauker SG. (1998) Pretreatment evaluation of chronic hepatitis C. *Journal of the American Medical Association* 280:2088-2093.	No
31	Wong JB, and Koff RS, for the International Hepatitis Interventional Therapy Group. (2000) Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Annals of Internal Medicine* 133:665-675.	No
32	Younossi ZM, Singer ME, McHutchison JG, Shermock KM. (1999) Cost effectiveness of interferon a2b combined with ribavirin for the treatment of chronic hepatitis C. *Hepatology* 30:1318-1324.	No
33	Yuan Y, Iioeje U, Li H et al. (2008a) Economic implications of entecavir treatment in suppressing viral replication in chronic hepatitis B (CHB) patients in China from a perspective of the Chinese social security program. *Value in Health* 11 (Suppl 1): S11-S21	Yes
34	Yuan Y, Iioeje U, Hay J (2008) Evaluation of the cost-effectiveness of Entecavir versus lamivudine in hepatitis BeAg-Positive chronic hepatitis B patients. *Journal of Managed Care Pharmacy* 14(1): 21-33	Yes

Data extraction
The publications listed above can be categorised into two groups:

- Primary studies where utility weights had been measured either using preference-based techniques directly (eg, standard gamble (SG) or time trade-off (TTO)) or using a well-validated multi-attribute instrument with inherent preference valuation (eg, Health Utilities Index, mark 2 or 3 (HUI-2 or HUI-3), Assessment of Quality of Life (AQOL), SF6D, EuroQol-5D (EQ5D index)).

- Secondary studies where the utility weight had been derived elsewhere and the source was a primary paper published in English. These were typically economic evaluations that had used utility weighs reported elsewhere in the literature.

Publications cited in the secondary studies as the source of utility weights were cross checked with the empirical studies. References to utility weights were also sourced from relevant systematic reviews. If not already present, these were retrieved and included.

Of the 22 included papers in the first search that reported utility weights for HCC, 15 were classified as secondary studies and are summarised in **Table 6**. Of the 12 papers included from the updated search 10 were classified as secondary studies and are also summarised in **Table 6**. These studies are primarily cost-effectiveness analyses of screening for HCC or management of patients with HCV/HBV.

Table 6: Extraction of HCC utility weights from secondary publications

#	Author (year)	Study type	Utility weight for HCC	Source of utility values for HCC
1	Arguedas (2003)	CEA of screening for HCC in patients with hepatitis C cirrhosis	0.20 (range 0.10-0.40)	Bennett (1997), Buti (2000), Kim (1997), Younossi (2001)
2	Buti (2000)	CEA of combination therapy for naïve patients with CHC	0.10	Bennett (1997), Wong (1998 - abstract)
3	Castelnuovo (2006)	CEA of testing for hepatitis C in former injecting drug users	0.40 (SE 0.056) (non-symptomatic) 0.41 (SE 0.056) (symptomatic)	Taken from a large UK liver transplantation study – Ratcliffe (2002)
4	Coon (2007)	CEA and CUA of surveillance of patients with cirrhosis [alcoholic liver disease (ALD)-, hepatitis B (HBV)- and C virus (HCV)-related], using periodic serum □-fetoprotein (AFP) testing and/or liver ultrasound examination, to detect HCC, followed by treatment with liver transplantation or resection, where appropriate.	0.64 (range 0.44-0.86)	Chong (2003)
5	Coon (2008)	CEA of surveillance for HCC in individuals with cirrhosis	0.64 (range 0.44-0.86)	Chong (2003)
6	Del Rio (2006)	CEA of haematologic growth factors for anaemia occurring during hepatitis C combination therapy	0.25 (0.10-0.80)	Singer (2001), Younossi (1999)
7	Enriquez (2007)	CEA of suppressing hepatitis B virus DNA in immune tolerant patients to prevent HCC and cirrhosis	0.72 (0.62-0.82)	Chong (2003)
8	Kanwal (2005)	CUA stratified by hepatitis B e antigen (HBeAg) status.	0.73 (0.5-0.8)	Chong (2003)
9	Law (2003)	Modelling of epidemiology and natural history of HCV in Australia to estimate HCV incidence and prevalence and project future trends in the long-term sequelae of HCV infection	0.10 (for diagnosed HCC)	Bennett (1997)
10	Lin (2004)	CEA of screening for HCC in patients with cirrhosis due to CHC	0.5 (range 0.2-0.7) (all Child-Pugh classes)	Bryce (1999), Marotta (1999), Younossi (2001)
11	Nouso (2008)	CEA of the surveillance of HCC in different medical circumstances	0.5 (0.15-0.95)	Lin (2004), Salomon (2003)
12	Patel (2005)	CEA of HCC surveillance in patients with HCV-related cirrhosis	0.3 (untreatable HCC) 0.8 (post-resection) 0.8 (post CLT) 0.8 (post LDLT)	Untreatable HCC – Bennett (1997), Kim (1997) Post-resection and post-liver transplantation utilities - estimated (assumed to be same as utility for compensated cirrhosis)

13	Salomon (2003)	CEA of the surveillance of HCC in different medical circumstances	0.5 (0.15-0.95)	Wong, 1998
14	Sarasin (2001)	CEA of LDLT vs CLT for early HCC	0.6 (HCC waiting for CLT) 0.8 (cured HCC after CLT) 0.5 (incurable HCC and cirrhosis)	Utility for incurable HCC - approximate based on values assessed in group of severely ill patients (Tsevat 1994). Liver transplantation utilities – Bravata (1999), Bryan (1998) HCC - Lynn (2000), Wong (2000)
15	Shepherd (2006)	Systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B	Literature: 0.118-0.490, Used in model: –0.54 (decrement to the age-specific health state utilities for healthy individuals)	Utilities in literature: Crowley (2000, 2002), Dusheiko (1995), Wong (1995), Mild Hepatitis C trial. For modelling used: Ratcliffe (2002), Wright (2005)
16	Shiell (1999)	CEA of treating HCV infection with IFN-alfa in Australia	0.25 (range 0.1-0.40)	Kim (1997)
17	Siebert (2003)	CEA of initial treatment of chronic hepatitis c with peginterferon α-2b plus ribavirin compared with interferon α-2b plus ribavirin.	0.860 (range 0.837-0.833)	GEHMO database (Siebert 2001) *
18	Singer (2001)	CEA of screening for HCV in asymptomatic, average-risk adults	0.25 (0.1-0.5)	Bennett (1997), Kim (1997)
19	Sinha (2000)	CEA of different strategies of management of CHC in children	0.5 (range 0.15-0.95)	Bennett (1997), Kim (1997)
20	Veenstra (2008a)	CUA of anti-viral treatment strategies for HBeAg-negative CHB	0.41 (range 0.36– 0.46)	Levy (2008)
21	Veenstra (2008b)	CEA of Peginterferon Alfa-2a Compared to Lamivudine	0.5 (range 0.3–0.5)	Pwu (2002)
22	Wong (2000)	CEA of watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild CHC	0.55 (SD 0.20)	Wong (1998)
23	Younossi (1999)	CEA of IFN a2b combined with ribavirin for the treatment of CHC	0.25 (range 0.1-0.5) 0.50 (after 1st year)	Bennett (1997), Kim (1997)
24	Yuan (2008a) Value Health	CEA of entecavir treatment compared to lamivudine	0.30 (range 0.73)	Levy (2008), Kanwal (2005)
25	Yuan (2008b) J Manag Care Pharm	CEA of entecavir Versus Lamivudine in Hepatitis BeAg-Positive Chronic Hepatitis B Patients	0.41	Levy (2008)

*Siebert 2001 was cited as the source of the utility values, however in the published conference abstract, these values were not found. Presentation was not available.
Abbreviations: HBeAg=hepatitis B e antigen, CEA=cost-effectiveness analysis, CUA=cost-utlity analyisCHC=chronic hepatitis C, CLT=cadaveric liver transplantation, HCC=hepatocellular carcinoma, HCV=hepatitis C virus, IFN=interferon, LDLT=living donor liver transplantation, SD=standard deviation, SE=standard error

The literature search identified seven primary studies from the first search and 2 from the updated search that measured preference-based utility weights directly (**Table 7**). Note that although several of the secondary studies referenced a publication by Kim *et al.* (1997), this study obtained a utility weight for HCC from a panel of hepatologists (number not reported) and one nurse specialist, using "a generic instrument" which was referenced as the 1987 book by Drummond *et al*. Since the method of utility derivation was not reported, this study was not considered eligible for inclusion. Siebert 2001, referenced as a primary study, was only available in abstract format. As the abstract did not include utility values, it was not included in the review.

Data were extracted regarding the method of utility weight elicitation, including whether the health state related to the patients health state at the time or to a hypothetical scenario. Within all studies, data were extracted relating to any HCC health state. This included data relating to different points in time, stage of disease, and different interventions. Where the validation was undertaken by persons other than the patients, these details were recorded. Details of the instrument or method used were extracted.

Table 7: Summary of characteristics of primary studies reporting HCC utility weights

#	Author (year)	Study type	Country	Participants	Method of utility derivation	Health state/s	From updated search
1	Bennett (1997)	CEA of IFN-2b in patients with mild CHC	United States	Panel of hepatologists (N=6)	TTO on a scale of 0 to 10, using hypothetical health state descriptors	Mild CHC, moderate CHC, compensated cirrhosis, ascites, VH, HE, **HCC**, liver transplantation (first year/after first year), IFN-α2b (short-term)	No
2	Chong (2003)	Study to derive HCV utilities directly from patients with the health state	Canada	Consecutive HCV outpatients (N=178) and consecutive outpatients with **HCC from any aetiology (N=15)** HCC aetiology: 7 HCV, 4 HBV, 3 alcoholic liver disease, 1 haemochromatosis. Mean age: 63 yr (SE 2.7), Male: 14 (93%), White 7 (54%), Cancer treatment: 6 (40%), Remission: 1, Mean time since diagnosis: 1.1 yr (SD 1.3), Child-Pugh A/B/unknown: 10/4/1 Metastases: 2 (13%)	SG, HUI 3 [a], EuroQol Index [a], elicited directly from patients with the health state. Comparison with published utilities from experts – Dusheiko (1995), Bennett (1997), Kim (1997), Wong (1998), Shiell (1999), Younossi (1999), Sinha (2000), Pereira (2000), Singer (2001).	No liver biopsy, mild/moderate chronic infection, compensated cirrhosis, decompensated cirrhosis, HCC (demonstrated by liver biopsy or CT scan), liver transplant, SVR (to IFN ± ribavirin therapy)	No
3	Crowley (2000)	CEA of lamivudine for the treatment of CHB	Australia	Members of an expert panel (N=4)	AQoL, using hypothetical health state descriptors. Sensitivity analysis using estimates from literature – Bennett (1997), Dushieko (1995), Wong (1995)	Chronic hepatitis (on treatment with lamivudine/ IFN-alpha/ no treatment), seroconverted, compensated cirrhosis, decompensated cirrhosis (ascites/ VH/ HE, **HCC**	No
4	Levy et al. 2008	Utility study	US, Canada, United Kingdom, Spain, Hong Kong, and mainland China	Hepatitis patients and uninfected respondents (primarily recruited from staff and students at local universities as well as the population at large).	Standard Gamble interview with patients and non-infected respondants	Chronic Hepatitis B, compensated and decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation within and after the first year.	Yes
5	Pwu	CEA of IFN-α	Taiwan	Taiwanese hepatologists	TTO, elicited	HBsAg+/HBeAg+,	No

#	Author (year)	Study type	Country	Participants	Method of utility derivation	Health state/s	From updated search
	(2002)	therapy in the treatment of CHB in Taiwan		(N=12) and patients with liver disease (N=53). HCC utility weight from 1 patient with HCC	directly from patients with the health state, but clinicians given hypothetical health state descriptors	HBsAg+/HBeAg-, chronic hepatitis, compensated cirrhosis, decompensated cirrhosis, **HCC**, IFN (short term)	
6	Siew (2008)	Study to determine the relationship between HRQoL and stages of chronic hepatitis B infection compared with normal and with a disease control.	Singapore	Patients with chronic HBV, defined as having hepatitis B surface antigen positive for more than 6 months. A total of 432 HBV (156 asymptomatic carriers, 142 chronic hepatitis B, 66 compensated cirrhosis, 24 decompensated cirrhosis, 22 hepatocellular carcinoma, and 22 post–liver transplant) patients, 93 hypertensive patients, and 108 normal controls.	EQ-5D and SF-36 to estimate utility for disease state.	Hepatitis B, hypertension, controls, asymptomatic carriers, chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and post–liver transplant	Yes
7	Wells (2004)	Study to compare HR-QOL preferences in physicians and cirrhotics for 6 health states associated with cirrhosis	United States	Housestaff and staff physicians who regularly encounter patients with cirrhosis (N=83), and consecutive outpatients with diagnosed cirrhosis who had not undergone transplantation (N=114) Mean age: 52 yr (SD 9), Caucasian: 85 (75%), Male: 67, Child-Pugh A/B/C: 32%/52%/16% Hepatitis C: 62 (54%)	TTO (on a scale of 0 to 1), using hypothetical health state descriptors	Compensated cirrhosis, decompensated cirrhosis, decompensated cirrhosis with HE/ or VH/ or SBP, or **cirrhosis with HCC** [b]	No
8	Wong (1995)	CEA of IFN-2b treatment for hepatitis B e antigen-positive CHB	United States	Expert panel (N= 8)	SG and TTO (averaged), using hypothetical health state descriptors	HBsAg+/HBeAg+, HBsAg+/HBeAg-, chronic hepatitis, compensated cirrhosis, decompensated cirrhosis, **HCC**, IFN (short term)	No
9	Wong (1998)	CEA of alternative pre-treatment management strategies for patients with CHC	United States	Expert panel of senior hepatologists familiar with liver disease and IFN treatment, who received a description of the modelled health states (N=6)	SG and TTO, on a scale of 0 to 1, using hypothetical health state descriptors	Positive for HCV, mild CHC, moderate CHC, compensated cirrhosis, ascites (diuretic sensitive/ refractory), VH, HE, **HCC**	No

Abbreviations: AQoL=Assessment of Quality of Life, CHB=chronic hepatitis B, CHC=chronic hepatitis C, *CLT=cadaveric liver transplantation, CUA=cost-effectiveness analysis, HBeAg=hepatitis B early antigen, HBsAg=hepatitis B surface antigen, HCC=hepatocellular carcinoma, HCV=hepatitis C virus, HE= hepatic encephalopathy, HR-QOL=health-related quality of life, HRQoL=health-related quality of life HUI 3=Health Utilities Index Mark 3, IFN=interferon, LDLT=living donor liver transplantation, SBP= spontaneous bacterial peritonitis, SG=standard gamble, SVR=sustained virologic response, TTO=time trade-off, unk=unknown, VH=variceal haemorrhage, EQ-5D=EuroQol 5 Dimensions, SF-36=Short-Form 36 Health Survey*
a Domains of health stratified into three to five levels. Utilities for each health state were measured from randomly sampled members of the community. HUI 3 norms were based on a mail survey of 7509 Canadians who reported no comorbidities. EuroQol norms were based on a mail survey of 1518 Canadians living in Alberta, including those with comorbidities.
b Health state description for cirrhosis with HCC: "Consider a 12-month period of life in which you have cirrhosis. In addition, you have a type of cancer of the liver called hepatocellular carcinoma, which may cause worsening fatigue and abdominal pain. You may have developed complications such as jaundice (yellowing of the skin), bleeding varices (blood vessels in your throat and stomach), ascites (fluid accumulation in your abdomen, which causes increased weight and bloating, which may interfere with your breathing), and encephalopathy (confusion). Your chance of death in the next year is 80%." The trade-off was "How many months of full health are of equal value to 12 months in the health state?"

Table 8 presents the HCC utility weights reported in each of the nine primary studies. Data relating to both mean and median, and appropriate measures of variance, were extracted wherever they were reported.

Table 8: Extraction of HCC utility weights from primary publicationsAbbreviations:
AQoL=Assessment of Quality of Life, CHB=chronic hepatitis B, CHC=chronic hepatitis C, CI=confidence interval,

#	Author (year)	HCC health state	Utility instrument	Central estimate of utility for HCC	Variance
1	Bennett (1997)	HCC (as a health state for CHC)	TTO	Median 0.10	Range 0.02-0.50
2	Chong (2003)	HCC (as a health state for CHC)	SG	Mean 0.72	95% CI 0.62-0.82
			HUI 3	Mean 0.51	95% CI 0.26-0.76
			EuroQol	Mean 0.65	95% CI 0.44-0.86
			Literature estimates (after 1st year)	0.10-0.80	
3	Crowley (2000)	HCC (as a health state for CHB)	AQoL	0.118	Literature estimates: 0.10-0.49
4	Levy et al. 2008	HCC (independent and as health state for CHB)	SG: uninfected respondants	0.41	95% CI: 0.39–0.43
			SG: infected respondents	0.38	95% CI: 0.36–0.41
5	Pwu (2002)	HCC (as a health state for CHB)	TTO: patient-elicited (n=1)	0.5	-
			TTO: physician utilities	Median 0.5	25th percentile 0.33 75th percentile 0.75
6	Siew (2008)	HCC (as health state for CHB)	EQ-5D	EQ-5D: Median: 0.83 EQ-5D VAS: 70.00	EQ-5D: 25th percentile 0.73 75th percentile 1.00 EQ-5D VAS: 25th percentile 50 75th percentile 85.75
			SF-36	PCS: Median 45.27 MCS: Median 43.10	PCS: 25th percentile 37.34 75th percentile 54.45 MCS: 25th percentile 33.95 75th percentile 47.34
7	Wells (2004)	Cirrhosis with HCC	TTO: patient-elicited	Mean 0.30 Mean 0.28 (Child-Pugh A) Mean 0.30 (Child-Pugh B) Mean 0.31 (Child-Pugh C)	SD 0.29
			TTO: physician utilities	Mean 0.19	SD 0.12
8	Wong (1995)	HCC (as a health state for CHB)	SG and TTO (averaged)	Mean 0.490	0.14-0.84 (range used in analysis)
9	Wong (1998)	HCC (as a health state for CHC)	SG and TTO	0.55	0.15-0.95 (range used in analysis)

HCC=hepatocellular carcinoma, HUI 3=Health Utilities Index Mark 3, NR=not reported, SD=standard deviation, SE=standard error, SG=standard gamble, TTO=time trade-off, VAS=visual analogue scale, PCS= physical component summary: MCS= mental component summary

The utility values in the secondary publications ranged between 0.10-0.95, and were used in different subgroups of patients with hepatitis C or B, liver cirrhosis or liver transplantation. Similarly the health states for HCC used in the primary publications were for subgroups of HCC patients with hepatitis C or B or cirrhosis, with average utilities ranging from 0.10 to 0.80. Only Levy et al. (2008) reported utility values for HCC without hepatitis C or B or cirrhosis, with the help of standard gamble interviews. However the description of the HCC health state assumes that some patients are taking chemotherapy, and experiencing AEs and additional hospital visits due to this therapy. As a result, the utility value elicited applies to a subset of patients taking chemotherapy. Thus the literature did not provide appropriate utility values for the relevant patient population but only for specific subgroups with a very wide range of utilities.

Appendix: Excluded publications from literature search for HCC utility weights

From the first search in January 2008 26 potentially relevant publications were identified in the search of EMBASE and MEDLINE. Seven publications were excluded after review of title and abstract and another four were excluded after review of the full publication. From the updated search another four publications were excluded after review of the full publication. The citations and abstract (if available) of all 15 excluded publications is shown below, annotated with reason for exclusion.

1. Biancofiore G. (2007) Economics and organ transplantation: A challenge to win. *Minerva Anestesiologica* 73:487-488.
   Notes: Abstract/title: Excluded. Wrong publication type

2. Chin BB and Chang PPL. (2006) Gastrointestinal malignancies evaluated with 18F-fluoro-2-deoxyglucose positron emission tomography. *Best Practice and Research in Clinical Gastroenterology* 20:3-21.
   Abstract: 18F-fluoro-2-deoxyglucose positron emission tomography has demonstrated high accuracy in the staging and evaluation of colorectal and esophageal carcinomas. FDG PET is demonstrating increasing utility in a number of other gastrointestinal tumours and clinical scenarios. The established clinical indications for its use, the diagnostic accuracy, and limitations will be reviewed. Data on the emerging indications and limitations for pancreatic, hepatocellular, and gastric carcinomas, as well as gastrointestinal stromal tumours, cholangiocarcinoma, and carcinoma of unknown primary will also be briefly discussed. The use of combined PET-CT is demonstrating further improvements in diagnostic accuracy. (copyright) 2005 Elsevier Ltd. All rights reserved
   Notes: Abstract/title: Excluded. Wrong indication (not HCC)

3. Dan, Y. Y., M. O. Aung, et al. (2008). "The economics of treating chronic hepatitis B in Asia." *Hepatology International* 2(3): 284-295.
   Chronic hepatitis B constitutes a significant health and economic burden to Asian countries.
   Six medications are now approved for the treatment of chronic hepatitis B, but there is still significant uncertainty with regards to treatment outcomes, cost impact, and benefits in view of the absence of long-term outcomes data. Cost-effectiveness Markov modeling thus allows us to project and estimate long-term outcomes based on current data and compare the cost-benefit between different treatment options. However, there are limitations to these reported studies. Cost-utility indices such as cost/quality-adjusted life years (cost/ QALY) may not be intuitive to clinicians and patients. These studies are also usually based on first-world economies, using a benchmark of US$50,000/QALY, and cannot be extrapolated directly to Asia-Pacific countries. Cost-effectiveness of various treatment strategies using a combination of cost-effectiveness indices may provide a more complete picture. These include cost/HBeAg seroconversion for HBeAg-positive patients (range: US$19,400-30,800) and cost/HBV DNA negative (PCR assay) for HBeAg-negative patients (range: US$14,400-32,000) over 5-year time horizon; cost per cirrhosis prevented (range: US$326,000-686,000) and cost per HCC prevented (range: US$654,000-1,380,000) over 10-year horizon using data from REVEAL study, cost per end point complication prevented in cirrhotics (US$9,630/year), and cost per HCC prevented in cirrhotics (US$ 27,600/year) over a 32-month horizon, using data from Asia Lamivudine Cirrhosis Study. More potent antivirals with low resistance appear to have lower cost/clinical end point averted. Published reports of cost-utility analysis comparing treatment using conventional cost/QALY show that all treatment modalities fall below the first-world benchmark of US$50,000/QALY but vary in modeling assumptions and in quality, making comparisons difficult. Reimbursement policies affect out-of-pocket expenses to the patient, and increases the proportion of patients who can afford therapy, but generally do not affect cost-effectiveness. In conclusion, cost-effectiveness analysis is an important tool for health care administrators, clinicians, and patients to decide on the optimal therapy for chronic hepatitis B, but the methodology permits considerable leeway for interpretation of results, thus a combination of cost-effective indices may be needed to paint a more complete picture. (copyright) Asian Pacific Association for the Study of the Liver 2008.
   Notes: Abstract/title: Excluded. Wrong indication (not HCC)

4. Dan YY and Lim SG. (2007) Applicability of cost-effectiveness analysis to management of chronic hepatitis B. *Journal of Gastroenterology and Hepatology* 22:1357-1359.
   Notes: Abstract/title: Excluded. Wrong publication type

5. De Simone P, Vignali C, Petruccelli S, Carrai P, Coletti L, Montin U, Catalano G, Urbani L, and Filipponi F. (2006) Cost Analysis of Tumor Downsizing for Hepatocellular Carcinoma Liver Transplant Candidates. *Transplantation Proceedings* 38:3561-3563.
   Abstract: We report the results of a prospective, intent-to-treat (ITT) trial on the costs of selective tumor downsizing (DS) before liver transplantation (LT) for patients affected with hepatocellular carcinoma (HCC). The trial started in January 1997 including adult patients with nodular-type HCC within and beyond the Milan criteria. Patients were downsized with transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI) and/or radiofrequency ablation (RFA) according to clinical predictors. TACE and RFA were performed as inpatient procedures, while PEI was performed on an outpatient basis. Costs of DS were obtained according to the Tuscany Health Reimbursement Fee Catalog adjusted to yearly inflation rates from 1997 through 2005. Data analysis was performed at 1 year after the last enrollment of 198 patients, including 161 (81.3%) who were transplanted: 34 (17.2%) dropped out and 3 (1.5%) were still on the waiting list. One hundred and fifty-two patients (76.7%) underwent DS for a total of 201 procedures: 159 TACE, 39 PEI, and 3 RFA. Overall costs in Euros ((euro)) of waitlisting were 861,801.24(euro): 548,460(euro) (63.7%) for pretransplantation evaluation; 197,994.84(euro) (22.9%) for control visits and hospitalizations; and 115.346.4(euro) (13.4%) for DS. Mean costs of DS were 758.58(euro) (plus or minus) 270(euro) per downstaged patient (747.53(euro) (plus or minus) 257.1(euro) Milan; 774.01(euro) (plus or minus) 287.71(euro) non-Milan); 582.85(euro) (plus or minus) 398.87(euro) per waitlisted patient (520.28(euro) (plus or minus) 406.23(euro) Milan; 520.28 (plus or minus) 364.48(euro) non-Milan); and 716.4(euro) per transplanted patient (580.67(euro) Milan; 1026.76(euro) non-Milan; +76.8%). A selective policy of tumor DS increased the costs of LT waitlisting by 13.4%, but due to higher dropout rates among non-Milan patients, the cost utility of DS was 76.8% higher in the Milan group. (copyright) 2006 Elsevier Inc. All rights reserved
   Notes: Abstract/title: Included. Full publication: Excluded. Utility weights not reported

6. Everson GT. (2000) Increasing incidence and pretransplantation screening of hepatocellular carcinoma. *Liver Transplantation* 6:S2-S10.
   Abstract: Key Points. 1. The incidence of hepatocellular cancer (HCC) in the United States and other traditionally 'low-incidence' countries is increasing. 2. The rise in incidence of HCC is related to chronic hepatitis C. 3. Timely performance of liver transplantation is curative in patients with early-stage HCC. 4. Cirrhotic patients, especially those with viral hepatitis, should be screened for HCC. 5. The performance characteristics of current tests are suboptimal, but serial ultrasonography and alphafetaprotein are recommended. 6. Estimated medical charges related to

screening and treatment suggest that $285,294 is required per 'cured' case. Assuming that this cure is associated with a 75% to 85% chance for high-quality 10-year survival, the charges approximate $35,000 to $40,000/quality-adjusted life-year (QALY). This cost-benefit analysis is nearly identical to published rates for breast cancer screening ($30,000/QALY)
Notes: Abstract/title: Included. Full publication: Excluded. Wrong publication type

7. Komandnri S and Cotler SJ. (2002) Hepatitis C. *Clinical Perspectives in Gastroenterology* 5:91-99.
Abstract: Although the incidence of new cases has decreased by more than 80% the past decade, hepatitis C-related complications and financial costs are projected to increase substantially because of the large reservoir of infection in young people and the need for liver transplantation in many. Older age at infection, alcohol abuse, male gender, and HIV coinfection are associated with rapid disease progression. Evaluation of liver histology best identifies the risk of developing cirrhosis. Combination therapy with interferon and ribavirin can yield a sustained remission in genotype 2 or 3 as high as 80%, but only half that for genotype 1. Novel future approaches might involve cleaving ribosomes, targeted antivirals, and polymerase and helicase inhibitors
Notes: Abstract/title: Excluded. Wrong publication type

8. McLernon, D. J., J. Dillon, et al. (2008). "Systematic review: Health-state utilities in liver disease: A systematic review." Medical Decision Making 28(4): 582-592. Yes just to be sure
Objectives. Health-state utilities are essential for cost-utility analysis. Few estimates exist for liver disease in the literature. The authors' aim was to conduct a systematic review of health-state utilities in liver disease, to look at the variation of study designs used, and to pool utilities for some liver disease states. Methods. A search of MED-LINE, EMBASE, and CINAHL from 1966 to September 2006 was conducted including key words related to liver disease and utility measuring tools. Articles were included if health-state utility tools or expert opinion were used. Variance-weighted mean utility estimates were pooled using metaregression adjusting for disease state and utility assessment method. Results. Thirty studies measured utilities of liver diseases/disease states. Half of these estimated utilities for hepatitis viruses: hepatitis A (n = 1), hepatitis B (n = 4), and hepatitis C (n = 10). Others included liver transplant (n= 6) and chronic liver disease (n= 5) populations. Twelve utility methods were used throughout. The EQ-5D (n = 10) was most popular method, followed by visual analogue scale (n = 9), time tradeoff (n = 6), and standard gamble (n = 4). Respondents were patients (n= 16), an expert panel (n = 10), non-liver diseases adults (n=2), patient and expert (n = 1), and patient and healthy adult (n = 1). Type of perspective included community (n=21), patient (n=4), and both (n = 5). The pooled mean estimates in hepatitis C with moderate disease, compensated cirrhosis, decompensated cirrhosis, and post-liver transplant using the EQ-5D were 0.75, 0.75, 0.67, and 0.71, respectively. The change in these utilities using different methods were -0.07 (visual analogue scale), -0.01 (health utilities index version 3), +0.04 (standard gamble), + 0.08 (health utilities index version 2), + 0.12 (time tradeoff), and + 0.15 (standard gamble-transformed visual analogue scale). Conclusions. The authors have created a valuable liver disease- based utility resource from which researchers and policy makers can easily view all available utility estimates from the literature. They have also estimated health-state utilities for major states of hepatitis C.
Notes: Abstract/title: Included. Full publication Utility weights not reported

9. Merchante N, Jimenez-Saenz M, and Pineda JA. (2007) Management of HCV-related end-stage liver disease in HIV-coinfected patients. *AIDS Reviews* 9:131-139.
Abstract: End-stage liver disease due to hepatitis C virus has become a major challenge in the management of HIV/HCV-coinfected patients. The diagnosis and management of cirrhosis and its complications in the scenario of HIV/HCV-coinfection are reviewed. Noninvasive approaches to the diagnosis of cirrhosis, such as biomarkers or transient hepatic elastography, may be considered. The clinical profile of cirrhosis decompensation in the coinfected population is different from that found in HCV-monoinfected individuals. Ascites and hepatic encephalopathy are much more frequent, whereas hepatocellular carcinoma is still uncommon, when simultaneous hepatitis B virus infection is absent. The newest and more conflicting topics on the management of these complications are also discussed. Liver transplantation seems to be a proper option of treatment in HIV/HCV-coinfected patients and should be considered early in their management, since mortality after the first hepatic decompensation is high
Notes: Abstract/title: Excluded. Wrong publication type

10. Sagmeister M, Mullhaupt B, Kadry Z, Kullak-Ublick GA, Clavien PA, and Renner EL. (2002) Cost-effectiveness of cadaveric and living-donor liver transplantation. *Transplantation* 73:616-622.
Abstract: Background. Cadaveric liver transplantation (5-year survival >80%) represents the standard of care for end-stage liver disease (ESLD). Because the demand for cadaveric organs exceeds their availability, living-donor liver transplantation has gained increasing acceptance. Our aim was to assess the marginal cost-effectiveness of cadaveric and living-donor orthotopic liver transplantation (OLT) in adults with ESLD. Methods. Using a Markov model, outcomes and costs of ESLD treated (1) conservatively, (2) with cadaveric OLT alone, and (3) with cadaveric OLT or living-donor OLT were computed. The model was validated with published data. The case-based scenario consisted of data on all 15 ESLD patients currently on our waiting list (3 women, 12 men; median age, 48 years [range, 33-59 years]) and on the outcome of all OLT performed for ESLD at our institution since 1995 (n=51; actuarial 5-year survival 93%). Living-donor OLT was allowed in 15% during the first year of listing; fulminant hepatic failure and hepatocellular carcinoma were excluded. Results. Cadaveric OLT gained on average 6.2 quality-adjusted life-years (QALYs) per patient compared with conservative treatment, living-donor OLT, an additional 1.3 QALYs compared with cadaveric OLT alone. Marginal cost-effectiveness of a program with cadaveric OLT alone and a program with cadaveric and living-donor OLT combined were similar ((euro) 22,451 and (euro) 23,530 per QALY gained). Results were sensitive to recipient age and postoperative survival rate. Conclusions. Offering living-donor OLT in addition to cadaveric OLT improves survival at costs comparable to accepted therapies in medicine. Cadaveric OLT and living-donor OLT are cost-effective
Notes: Abstract/title: Excluded. Wrong indication (not HCC)

11. Singal, A. and J. A. Marrero (2008). "Screening for hepatocellular carcinoma." Gastroenterology and Hepatology 4(3): 201-208.Hepatocellular carcinoma (HCC) currently has the fifth highest incidence rate among tumors worldwide, a rate expected to continue to increase over the next several decades. The majority of patients with HCC have cirrhosis of the liver, with chronic hepatitis B and C as the major agents of etiology. Despite advances in technology, the prognosis of patients with HCC has shown little improvement over time, most likely because most patients are diagnosed at advanced stages. HCC meets the criteria established by the World Health Organization for performing surveillance in those at risk for developing this tumor (ie, patients with cirrhosis of the liver). The objective of surveillance is to use a relatively simple and inexpensive examination in a large number of individuals to determine whether or not they are likely to develop cancer, with the overall goal of reducing morbidity and mortality from the cancer. In this article, we evaluate the criteria for performing surveillance for HCC and review the data on the efficacy of current surveillance programs.
Notes: Abstract/title: Included. Full publication Wrong publication type

12. Wolf DC. (2003) Screening for hepatocellular carcinoma: Is it cost-effective? *Liver Transplantation* 9:682-683.
Notes: Abstract/title: Excluded. Wrong publication type

13. Wong JB, Poynard T, Ling MH, Albrecht JK, and Pauker SG. (2000) Cost-effectiveness of 24 or 48 weeks of interferon (alpha)-2b alone or with ribavirin as initial treatment of chronic hepatitis C. *American Journal of Gastroenterology* 95:1524-1530.
Abstract: OBJECTIVE: Initial therapy with ribavirin and interferon (alpha)-2b results in a higher sustained virological response than interferon alone, but this regimen is expensive. We aimed to examine the cost-effectiveness of 24- or 48-wk initial treatment with combination therapy versus interferon alone for patients who have chronic hepatitis C. METHODS: Data from recent randomized clinical trials comparing combination therapy to interferon alone were applied to a previously published computer cohort simulation to project lifelong clinical and economic outcomes. Natural history and economic estimates were based on published literature, expert panel estimates, and actual variable cost and reimbursement data. RESULTS: Using treatment stopping rules, sustained viral negative response rates would be 33.1% and 39.8% for patients receiving 24 versus 48 wk of ribavirin/interferon, compared with 14.3% for 48 wk of interferon alone. Compared to the interferon alone strategy, 24 or 48 wk of combination therapy should prolong life expectancy by 1.4 to 2.0 yr at marginal cost-effectiveness ratios of $4400 to $5400 per discounted quality-adjusted life-year (DQALY) ginned. Compared to 24 wk of combination therapy, 48 wk of combination therapy should prolong life expectancy by 0.6 yr at a marginal cost-effectiveness ratio of $7700 per DQALY gained. The results were robust, with 24 or 48 wk of combination therapy remaining preferred and cost-effective in sensitivity analysis compared with interferon alone. CONCLUSION: For patients with chronic hepatitis C, 24 or 48 wk of ribavirin and interferon should prolong life and be cost-effective when compared with 48 wk of interferon alone. (C) 2000 Am. Coll. of Gastroenterology
Notes: Abstract/title: Included. Full publication: Excluded. No utility weights reported

14. Wong JB, Davis GL, McHutchison JG, Manns MP, and Albrecht JK. (2003) Economic and Clinical Effects of Evaluating Rapid Viral Response to Peginterferon Alfa-2b plus Ribavirin for the Initial Treatment of Chronic Hepatitis C. *American Journal of Gastroenterology* 98:2354-2362.
Abstract: OBJECTIVES: Evaluation of 12-wk viral response to initial antiviral therapy for chronic hepatitis C has been recommended to minimize antiviral-associated morbidity and costs. The aim of this study was to examine the economic and clinical effects of evaluating rapid viral response during antiviral therapy for treatment naive chronic hepatitis C patients. METHODS: We applied viral response and drug dosage from an international randomized clinical trial of ribavirin plus peginterferon alfa-2b or ribavirin plus interferon alfa-2b to a previously published computer cohort simulation to project lifelong clinical and economic outcomes. Natural history and economic estimates were based on published literature, expert panel estimates, and actual variable and reimbursement cost data. RESULTS: The assessment of 12-wk rapid viral response reduced antiviral treatment duration by 40-44% and anti-viral costs by 44-45% (savings of $15,116-16,268 for peginterferon plus ribavirin and $8300 for interferon plus ribavirin) compared to full 48-wk dosing. With the 12-wk evaluation, the marginal cost-effectiveness of peginterferon plus ribavirin versus interferon plus ribavirin was $13,600-22,800 compared with $14,600-25,000 per discounted quality adjusted life-year gained with the 24-wk evaluation. For genotype 1, hepatitis C infected patients, 12-wk testing for peginterferon plus ribavirin remaining preferred and cost-effective compared with interferon plus ribavirin. For genotype 2 or 3, hepatitis C infected patients, 12-wk testing yielded similar results to those of 24-wk treatment. CONCLUSIONS: Assessment of 12-wk viral response in genotype 1, hepatitis C infected patients should reduce peginterferon plus ribavirin morbidity and costs and improve its cost-effectiveness; however, for genotype 2 and 3, hepatitis C infected patients, 12-wk testing and 24-wk treatment have similar outcomes. Decisions regarding continuation of antiviral treatment should also consider the variability in the accuracy of quantitative viral assays as well as patient preferences and other potential benefits of the same treatments. (copyright) 2003 by Am. Coll. of Gastroenterology
Notes: Abstract/title: Included. Full publication: Excluded. No utility weights reported

15. You, J. H. S. and F. W. H. Chan (2008). "Pharmacoeconomics of entecavir treatment for chronic hepatitis B." Expert Opinion on Pharmacotherapy 9(15): 2673-2681.
Background: Entecavir is a new antiviral agent for chronic hepatitis B virus (HBV) infection with potent HBV suppression and a low rate of viral resistance. Objective: To review published studies on the pharmacoeconomics of entecavir for treatment of chronic HBV. Methods: A literature search on Medline and Embase over the period of 1998-2008 was performed in April 2008 using keywords 'entecavir' and 'cost'. Results/conclusion: Four studies comparing the cost effectiveness of entecavir with lamivudine and/or adefovir for treatment with chronic HBV infection using either decision tree or Markov modeling were reviewed. All four studies showed that entecavir was cost-effective in the treatment of chronic HBV with the incremental cost per QALY (quality-adjusted life-year) gained below the commonly accepted benchmark. The results are mainly due to the lower complication rates and better quality of life of patients using entecavir which can offset the higher acquisition cost of the drug. Patient characteristics, comparing agents and model assumptions were different among the four studies and they should be taken into account when applying the results to real life situations. (copyright) 2008 Informa UK Ltd.
Notes: Abstract/title: Included. Full publication No utility weights reported

10.12 Appendix 12: Utility mapping study

INTRODUCTION

Economic evaluation is a tool to assess whether health care interventions represent value for money to budget-holders. Cost-utility analysis is a type of economic evaluation that incorporates the preferences of individuals for different treatment-related outcomes (Torrance 1986, 1996). Utilities for a given health state represent the preference that individuals have for this health state (Torrance 1987). Utilities can be conceptualized as a single summary measure of health-related quality of life (HRQL) on a scale with the anchors of 1 corresponding to perfect health and 0 corresponding to death (Feeny et al. 1991; Torrance et al. 2002).

Utility measures can be obtained directly from clinical studies that include HUI or EQ-5D instruments to capture index utility scores. Guidance from the Washington panel on Cost-effectiveness in Health and Medicine, and more recently from NICE recommend that utilities are based on societal preferences of the general population (Gold et al 1996; NICE 2004). This can be achieved through interviews based on hypothetical health states with the general public, such as standard gamble (SG) and time-trade-off (TTO) interviews.

Most cancer clinical trials evaluate the impact of health care intervention on quality of life using cancer-specific questionnaires such as FACT or EORTC QLQ C-30. Kind et al (2005) and Bagust et al (2001) have used responses on these questionnaires to convert into a single utility index. Bagust et al (2001) converted the EORTC-QLQ-C30 questionnaire and its lung cancer module (LC-13) into a single utility index. Similarly Kind et al (2005) converted the FACT-L into a single index for use in the economic analysis of clinical trial data. The process of reducing such complex descriptive questionnaires into a single index involves determining the underlying structure and identifying the key items of each domain via statistical analysis. Factor analysis enables identification of which factors map onto the new shortened design. Other studies have converted more generic measures such as the SF-36 into utility measures using complex algorithms (Brazier et al. 2002).

Krabbe et al (2003) compared the generic HRQL questionnaire, the EQ-5D with the cancer specific EORTC-QLQ C30 for patients with liver cancer. Effect sizes were found to be comparable between the instruments, concluding that the EQ-5D algorithm can provide a summary measure that is as sensitive as the disease specific EORTC-QLQ C-30 in a clinical setting.

Recently, Dobrez et al (2007) have published an algorithm to convert responses to FACT-G to TTO utilities based on utilities for current health elicited from cancer patients. In cancer-based setting it has been discussed whether it may be desirable to have patient preferences for treatment alone or in conjunction with societal preferences. The algorithm developed by Dobrez et al will be useful to estimate utilities for cost-utility analysis in absence of societal weights. The goal of the current study is to use an algorithm developed by Dobrez et al. (2007) to map the Functional Assessment of Cancer Therapy—General (FACT-G) to TTO utilities for selected health states in advanced HCC patients.

Description of FACT-G

The FACT-G is a valid and reliable instrument for establishing HRQL in cancer patients and can be used in conjunction with the FACIT (Functional Assessment of Chronic Illness Therapy) group's cancer specific measurement instruments (Cella et al. 1993). It consists of four domains, covering Physical, Social & Family, Emotional, and Functional well-being. As a general rule the full scales are comprised of the FACT-G (the general version of the cancer-specific QOL measure) plus an additional subscale of disease-, treatment-, or condition-specific concerns. For instance, this study will use the FACT-HEP, a self-report instrument designed to measure health-related quality of life (HRQL) in patients with hepatobiliary cancers (Heffernan et al. 2002). The FACT-Hep consists of the 27-item FACT-G, which assesses generic HRQL concerns, and the newly validated 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues. However based on the algorithm by Dobrez et al. only 4 items from FACT-G part of FACT-Hep are utilized to calculate utilities.

METHODS

Data

The data for this analysis was gathered during the course of the Sorafenib HCC Assessment Randomized Protocol (SHARP) study, a randomized, double blind trial to evaluate the clinical benefits of sorafenib versus placebo in subjects with advanced hepatocellular carcinoma (HCC). Subjects were randomized to receive either sorafenib at a dose of 400 mg (2 x 200 mg tablets) twice daily (bid), or matching placebo bid. The study showed a statistically significant increase in overall survival for soraefnib as compared to placebo. Quality of life data in Hepatocellular Carcinoma (HCC) patients was also collected at baseline and at the start of the third cycle (i.e. after 12 weeks based on 6 weekly cycles), using the Functional Assessment of Cancer Therapy- Hepatobiliary (FACT-HEP) questionnaire and the Physical and Functional Well-Being Subscales (PWB/FWB). This data will be used to derive utilities.

Calculation of utility values

The algorithm developed by Dobrez et al. (2007) was based on directly elicited TTO utilities provided by a large sample of cancer patients for their current health state and who also completed the FACT-G. The construction and testing of the algorithm to map FACT-G responses onto TTO utilities was conducted in four steps.

First, the eligible sample was randomly divided into algorithm construction and validation samples of equal size. Using the construction sample, FACT-G questions and response categories were then selected to maximize the model's expected predictive ability over a wide range of utility scores. Multiple regression models were explored to test for possible differences in predictive ability. The selected model was estimated using the construction sample. Finally, out-of-sample predictive ability was estimated using multiple groupings of subjects in the validation sample.

Use of the algorithm to estimate utilities requires that response categories first be collapsed, and converted in to sets of dummy variables for application of the regression equation. This is accomplished using the cross-walk equation below. All variables must be ordered so that a 0 indicates the worst possible response, so that two of the selected questions (physical well-being [PWB]: lack of energy and PWB: feel sick) should be reversed first.

$$\text{Utility}=1+\begin{pmatrix} -0.222 & if & q1 & = & (0 & , & 1) \\ -0.1137 & if & q1 & = & (2 & , & 3) \end{pmatrix} + \text{ (-.1537 if q2=0) + }$$

$$\text{(0.0431 if q3 =[0,1])+}\begin{pmatrix} -0.1254 & if & q4 & = & (0 & , & 1) \\ -0.0641 & if & & q4 & = & 2 & \\ -0.0345 & if & & q4 & = & 3 & \end{pmatrix}$$

Where q1 = PWB: lack of energy, q2 = PWB: feel sick, q3 = FWB: able to work, and q4 = FWB: able to enjoy life. Utilities are estimated by first calculating individual predicted utilities, and then averaging within the health states. (For the coding of utilities see Appendix 1).

Health States

A number of disease states in Hepatocellular Carcinoma (HCC) were developed for which utility values were required. The following health states were considered:

1 - stable patients, before progression according to investigator assessment with/without AEs

a - for best supportive care

b - for sorafenib patients

2 - stable patients, before progression according to hybrid assessment with/without AEs

a - for best supportive care

b - for sorafenib patients

3 - progressed patients according to investigator assessment with/without AEs

a - for best supportive care

b - for sorafenib patients

4 - progressed patients according to hybrid assessment with/without AEs

a - for best supportive care

b - for sorafenib patients

The overall QoL as measued by FACT-G part of Functional Assessment of Cancer Therapy—Hepatobiliary (FACT-HEP) instrument will be mapped to time trade-off (TTO) utilities for the above mentioned health states. Time points at which PWB/FWB have been collected are at baseline and start of cycle 3. Observations in each health state will be determined by combining patients at baseline and cycle 3 by following assumptions:

- Stable patients at baseline - If time to progression (TTP) for a patient is non-missing and greater than 1 then that patient is stable at baseline otherwise the patient has progressed at baseline .
- Stable patients at cycle 3 - If time to progression (TTP) is greater than the day of first cycle 3 visit relative to start of treatment then the patient is stable at cycle 3 otherwise the patient has progressed at cycle 3. For patients where day of first cycle 3 visit is missing the mean value for the whole population is substituted.
- In order to determine patients with and without grade 3 or 4adverse events, the following two scenarios are considered:
    1. Only those AEs reported in at least 10% of the sorafenib treated patients and considered to have consequences for patients' quality of life by expert clinicians were included in the analysis: rash/desquamation, hypertension, fatigue, weight loss, alopecia, diarrhoea, nausea/vomiting, hand-foot skin reaction and pain, abdomen.
    2. All grade 3 and 4 adverse events
- Patients without AE at baseline – If grade 3 or 4 (above mentioned) adverse events happened 30 days prior to answering the baseline FACT-HEP questionnaire or the number of days between answering baseline FACT-HEP question and start of AE is missing then that patients is considered to have an AE at baseline other wise the patient is without AE at baseline.
- Patients without AE at cycle 3 – If grade 3 or 4 (above mentioned) adverse events happened 30 days prior to answering the cycle 3 FACT-HEP question or the number of days between answering cycle 3 FACT-HEP question and start of AE is missing then that patients is considered to have an AE at cycle 3 otherwise the patient is without AE at baseline.

RESULTS

The results are shown in the following Tables 1-4.

Table 1 – Utility summary statistics for health states without selected grade 3 and 4 adverse events

Health state characteristics				Utility		
Health State descriptions	**Treatment arm**	**Number of observations**	**Number of patients**	**Mean**	**SD**	**Range**
1- Stable patients, before progression according to investigator assessment without AEs	a-for best supportive care	323	237	0.6818	0.1191	0.4996-1.0000
	b-for sorafenib patients	307	225	0.6957	0.1172	0.4996-0.9790
	All patients	*630*	*462*	*0.6885*	*0.1183*	*0.4996-1.0000*
2- Stable patients, before progression according to hybrid assessment without AEs	a-for best supportive care	302	237	0.6772	0.1180	0.4996-1.0000
	b-for sorafenib patients	290	222	0.6924	0.1196	0.4996-0.9790
	All patients	*592*	*459*	*0.6846*	*0.1189*	*0.4996-1.0000*
3- Progressed patients according to investigator assessment without AEs	a-for best supportive care	99	99	0.7094	0.1233	0.4996-0.9790
	b-for sorafenib patients	76	74	0.7132	0.1308	0.4996-1.0000
	All patients	*175*	*173*	*0.7111*	*0.1262*	*0.4996-1.0000*
4- Progressed patients according to hybrid assessment without AEs	a-for best supportive care	120	119	0.7162	0.1228	0.5427-1.0000
	b-for sorafenib patients	93	90	0.7203	0.1196	0.4996-1.0000
	All patients	*213*	*209*	*0.7180*	*0.1211*	*0.4996-1.0000*

Table 2 – Utility summary statistics for health states with selected grade 3 and 4 adverse events

				Utility		
Health State description	**Treatment arm**	**Number of observations**	**Number of patients**	**Mean**	**SD**	**Range**
1- Stable patients, before progression according to investigator assessment with AEs	a-for best supportive care	32	26	0.7140	0.1052	0.5600-0.8863
	b-for sorafenib patients	65	43	0.6888	0.1117	0.5427-0.8949
	All patients	*97*	*69*	*0.6972*	*0.1097*	*0.5427-0.8949*
2- Stable patients, before progression according to hybrid assessment with AEs	a-for best supportive care	33	28	0.7188	0.1050	0.5600-0.8863
	b-for sorafenib patients	61	43	0.6917	0.1148	0.5427-0.8949
	All patients	*94*	*71*	*0.7012*	*0.1117*	*0.5427-0.8949*
3- Progressed patients according to investigator assessment with AEs	a-for best supportive care	14	14	0.7469	0.1233	0.5600-1.0000
	b-for sorafenib patients	13	13	0.7263	0.1351	0.4996-0.9186
	All patients	*27*	*27*	*0.7370*	*0.1270*	*0.4996-1.0000*
4- Progressed patients according to hybrid assessment with AEs	a-for best supportive care	13	13	0.7373	0.1275	0.5600-1.0000
	b-for sorafenib patients	17	17	0.7071	0.1220	0.4996-0.9186
	All patients	*30*	*30*	*0.7202*	*0.1232*	*0.4996-1.0000*

Comparing mean utility values between Tables 1 and 2 it appears that utilities for health states with selected AEs are similar to those without selected AEs.

Table 3 – Utility summary statistics for health states without grade 3 and 4 adverse events

	Health state characteristics			Utility		
Health State description	**Treatment arm**	**Number of observations**	**Number of patients**	**Mean**	**SD**	**Range**
1- Stable patients, before progression according to investigator assessment without AEs	a-for best supportive care	291	213	0.6766	0.1185	0.4996-1.0000
	b-for sorafenib patients	260	189	0.6932	0.1168	0.4996-0.9790
	All patients	*551*	*402*	*0.6845*	*0.1179*	*0.4996-1.0000*
2- Stable patients, before progression according to hybrid assessment without AEs	a-for best supportive care	272	213	0.6717	0.1171	0.4996-1.0000
	b-for sorafenib patients	244	185	0.6885	0.1183	0.4996-0.9790
	All patients	*516*	*398*	*0.6797*	*0.1178*	*0.4996-1.0000*
3- Progressed patients according to investigator assessment without AEs	a-for best supportive care	86	86	0.6995	0.1221	0.4996-0.9790
	b-for sorafenib patients	65	63	0.6963	0.1312	0.4996-1.0000
	All patients	*151*	*149*	*0.6981*	*0.1257*	*0.4996-1.0000*
4- Progressed patients according to hybrid assessment without AEs	a-for best supportive care	105	104	0.7080	0.1225	0.5427-1.0000
	b-for sorafenib patients	81	79	0.7100	0.1230	0.4996-1.0000
	All patients	*186*	*183*	*0.7089*	*0.1224*	*0.4996-1.0000*

In Tables 1 and 3 within each health state the mean value of utility for patients treated with sorafenib are slightly higher than the patients who were treated with best supportive care although when taking into consideration the standard deviations and number of observations one would conclude that the results for the two treatments within each health states are similar.

Table 4 – Utility summary statistics for health states with grade 3 and 4 adverse events

				Utility		
Health State description	**Treatment arm**	**Number of observations**	**Number of patients**	**Mean**	**SD**	**Range**
1- Stable patients, before progression according to investigator assessment with AEs	a-for best supportive care	64	50	0.7214	0.1102	0.5600-0.9790
	b-for sorafenib patients	112	79	0.6973	0.1149	0.4996-0.9359
	All patients	*176*	*129*	*0.7060*	*0.1135*	*0.4996-0.9790*
2- Stable patients, before progression according to hybrid assessment with AEs	a-for best supportive care	63	52	0.7223	0.1101	0.5600-0.9790
	b-for sorafenib patients	107	79	0.7008	0.1195	0.4996-0.9655
	All patients	*170*	*131*	*0.7088*	*0.1162*	*0.4996-0.9790*
3- Progressed patients according to investigator assessment with AEs	a-for best supportive care	27	27	0.7606	0.1178	0.5427-1.0000
	b-for sorafenib patients	24	24	0.7661	0.1174	0.4996-0.9655
	All patients	*51*	*51*	*0.7632*	*0.1165*	*0.4996-1.0000*
4- Progressed patients according to hybrid assessment with AEs	a-for best supportive care	28	28	0.7570	0.1188	0.5427-1.0000
	b-for sorafenib patients	29	28	0.7412	0.1079	0.4996-0.9186
	All patients	*57*	*56*	*0.7490*	*0.1126*	*0.4996-1.0000*

Comparing mean utility values between Tables 3 and 4 indicates that progressed states with all the AEs reported have higher mean utility values than progressed and stable states without AE.

Looking across the health states in all four tables, the mean values of utility vary slightly and the patients with progression have higher utility values, although taking the number of observations and standard deviations into account progressed patients appear to have the same utility as stable patients.

Lastly, the mean utility values in Tables 1 and 3, and in Tables 2 and 4 indicate that the definition of AE does not affect mean utility values.

DISCUSSION

In cost-utility analysis utility values are required to estimate quality-adjusted life-years. A systematic review of utility in HCC found a total of 22 publications that reported utility weights for HCC. However, none of the studies distinguished between stable and progressive disease. Another systematic review (Pickard et al. 2007) reported only values for secondary HCC, where patients with colorectal liver metastasis were undergoing laparotomy. The SHARP trial which compared sorafenib to best supportive care in advanced HCC, assessed QoL using FACT-Hep Questionnaire. Recently, Dobrez et al. (2007) has published an algorithm using FACT-G to derive utilities based on patient preferences. This algorithm was used to elicit utilities in the current study for advanced HCC patients using quality of life data (as measured by FACT-Hep) obtained from SHARP trial.

The strength of the mapping algorithm by Dobrez et al. (2007) is that the mean values were well predicted for most subgroups as defined by ECOG-PS (Eastern Cooperative Oncology Group – Performance Status) and Short Form-36 physical functioning scores, and responses to the FACT-G overall quality of life item (mean absolute difference < 0.03, $P > 0.05$). The disadvantage of the algorithm is it is known that patient preferences are higher than societal preferences and over estimates the utility for poor health states. However as Dobrez et al point out such overestimation of utilities for poor health states has been reported even for algorithms that were based on community preferences. The results of the current study found that the mean utility values derived from the mapping algorithm were similar between the different health states and treatment arms, and the definition of adverse events did not influence the results. Only marginal differences were identified between patients with stable HCC and patients with progressive disease, and between patients with and without adverse events.

One possible explanation for similar utilities between stable and progressive patients could be due to the fact that the FACT-HEP values were collected relatively early in the SHARP trial – at baseline and at the beginning of the third six weekly cycle. Patients progressing may have been at the very beginning of progression, where the quality of life is still very similar to patients' in stable disease. Bukowski et al 2007 studied the impact of sorafenib on the QoL of patients with a different tumor type (RCC). Overall, no significant differences were found between the treatment group and a placebo group, although the sorafenib-treated patients did report significantly fewer symptoms and concerns on the FKSI single-items. In addition low sensitivity of algorithm to poor health states may have contributed to both health states having similar utilities.

The mean utility values were not affected by AE's. The FACT-HEP questionnaire was designed to assess the effect on quality of life due to health care interventions in HCC patients. One possible explanation may be that even though AE's were reported it did not affect their physical or functional well being i.e. the items included in this algorithm. Another explanation may be that FACT-Hep did not capture the effect of QoL. However this is unlikely given the instrument is reliable and has been validated before.

In conclusion, in absence of alternative utilities in HCC, this mapping algorithm provides utilities in HCC patients for use in cost-utility analysis for HCC interventions.

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10.13: Appendix 13: Resource use

CLINICIAN QUESTIONNAIRE

RESOURCE USE IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA PATIENTS

INTRODUCTION

Goal of This Survey: To obtain data about the resource use associated with the treatment of patients with non-curative hepatocellular carcinoma (HCC) in the UK. This information will be used to help develop a health economic model to evaluate treatment patterns for advanced HCC.

Patients: The questionnaire aims to cover patients with all aetiologies of hepatocellular carcinoma. We would like you to consider patients that meet the following inclusion/exclusion criteria (i.e. patients similar to the SHARP study population):

- Male or female patients > 18 years of age
- Patients who have a life expectancy of at least 12 weeks
- Patients with advanced HCC (histologically or cytologically documented)
- Patients must have at least one tumour lesion that has not been previously treated with local therapy (such as surgery, radiation therapy, hepatic arterial therapy, chemoembolisation, radiofrequency ablation, percutaneous ethanol injection or cryoablation)
- Patients who have an ECOG PS of 0, 1, or 2
- Cirrhotic status of Child-Pugh class A only

Excluding patients with:

- Renal failure requiring hemo- or peritoneal dialysis
- History of cardiac disease: congestive heart failure; cardiac arrhythmias; uncontrolled hypertension; myocardial infarction in past 6 months
- Active clinically serious infections (> grade 2)
- Known history of human immunodeficiency virus (HIV) infection
- Known Central Nervous System tumours including metastatic brain disease

Due to the individualised nature of treatment we recognise that it may be difficult to define a typical patient. However please provide estimates based on your experience.

Completion of the questionnaire:

- Please review the questionnaire prior to the telephone interview. Fill in as many questions in advance as possible to aid the discussion during the telephone interview. Some questions relate to the use of personal and social services and it may be necessary to consult the relevant member of the multidisciplinary team (e.g. nurse specialist, social worker) to assist with these answers.

- In all questions we ask about your own treatment practice, NOT about UK practice in general.
- Please provide your best estimates or best range of estimates.
- The interview should take less than 1 hour to complete. Please schedule enough uninterrupted time for the call.

Please do not hesitate to provide any additional comments throughout the questionnaire.

THANK YOU.

PATIENT BREAKDOWN

Approximately what proportion of all your HCC patients would be eligible for treatment with sorafenib based on the SHARP trial?

%

Thinking now of all your HCC patients who would be eligible for treatment with sorafenib according to the SHARP trial, what proportion fall into each of the following subgroups?

	Subgroups	**% of patients in subgroup**
Percentage of HCC patients eligible for treatment with sorafenib with;	TNM Stage I-III	
	Hepatitis C	
	No extrahepatic spread	
	No tumour burden	
	Age ≥ 65	
	BCLC Stage B	
	BCLC Stage C	
	Child Pugh A	
	Macroscopic vascular invasion	

MEDICAL STAFF CONTACTS

Thinking about all of your HCC patients with stable disease, which different types of health care professionals are they likely to visit for management of their disease?

How many times per month, if at all, would they see a typical HCC patient with stable disease being treated with sorafenib for the management of their disease?

And how many times per month, if at all, would they see a typical HCC patient with stable disease being treated with best supportive care for the management of their disease?

Medical staff contacts – for stable patients

Visits	**On Sorafenib**	**On Best Supportive Care**
At hospital:		
Appointment with **oncologist**		
Appointment with **hepatologist**		
Appointment with **specialist nurse**		
Appointment with **other (specify)**		
Community based health care:		
Appointment with **pain specialist**		
Appointment with **GP**		
Appointment with **district nurse**		
Appointment with **palliative care team** (consisting of?)		
Appointment with other (specify)		

Now thinking about all if your HCC patients with progressive disease, which different types of health care professionals are they likely to visit for the management of their disease?

How many times per month, if at all, would they see a typical HCC patient with progressive disease being treated with sorafenib for the management of their disease?

And how many times per month, if at all, would they see a typical HCC patient with progressive disease being treated with best supportive care for the management of their disease?

Medical staff contacts – for progressive patients

Visits	**On Sorafenib**	**On Best Supportive Care**
At hospital:		
Appointment with **oncologist**		
Appointment with **hepatologist**		
Appointment with **specialist nurse**		
Appointment with **other (specify)**		
Community based health care:		
Appointment with **pain specialist**		
Appointment with **GP**		
Appointment with **district nurse**		
Appointment with **palliative care team** (consisting of?)		
Appointment with other (specify)		

MONITORING/FOLLOW-UP OF PATIENTS

Thinking about all of your HCC patients with stable disease, which diagnostic tests (imaging and lab tests) / procedures are they likely to undergo for the monitoring of their disease?

For each of these tests, overall what proportion of your HCC patients with stable disease are receiving each type of test / procedure?

Generally, how many times per month would a typical HCC patient with stable disease undergo each type of diagnostic test / procedure? If the test is likely to be performed less than once a month enter a decimal e.g. if performed once every 3 months enter 0.333 (1 divided by 3).

Diagnostic procedures – stable patients

Diagnostic tests	% of stable patients receiving this procedure at your centre?	How often per month?
Imaging investigations		
Abdominal CT		
Abdominal MRI		
Abdominal Ultrasound		
Angiography		
Other (please specify):		
Laboratory tests		
Liver Biopsy		
Alpha-fetoprotein (AFP) test		
Liver function test		
INR		
Full blood count (FBC)		
Calcium (Ca^{++})		
Glucose		
Complete metabolic panel		
Other (please specify)		

Now thinking about all of your HCC patients with progressive disease, which diagnostic tests (imaging and lab tests) / procedures are they likely to undergo for the monitoring of their disease?

For each of these tests, overall what proportion of your HCC patients with progressive disease are receiving each type of test / procedure?

Generally, how many times per month would a typical HCC patient with progressive disease undergo each type of diagnostic test / procedure? If the test is likely to be performed less than once a month enter a decimal e.g. if performed once every 3 months enter 0.333 (1 divided by 3).

Diagnostic procedures – progressive patients

Diagnostic tests	% of stable patients receiving this procedure at your centre?	How often per month?
Imaging investigations		
Abdominal CT		
Abdominal MRI		
Abdominal Ultrasound		
Angiography		
Other (please specify):		
Laboratory tests		
Liver Biopsy		
Alpha-fetoprotein (AFP) test		
Liver function test		
INR		
Full blood count (FBC)		
Calcium (Ca^{++})		
Glucose		
Complete metabolic panel		
Other (please specify)		

HOSPITAL RELATED COSTS

For each of the different types of HCC patient listed please detail the resource use (including both inpatient and outpatient resources) due to their disease. Please note, this excludes any treatment relating to adverse events.

Inpatients and outpatient resource use for HCC patients due to disease (not treatment related adverse events)

	Stable patients on sorafenib	Stable patients on BSC *	Progressive patients on sorafenib	Progressive patients on BSC *
% of patients requiring no hospitalisation due to HCC per year				
% of patients requiring 1 hospitalisation due to HCC per year				
% of patients requiring 2 hospitalisations due to HCC per year				
% of patients requiring more than 2 hospitalisations due to HCC per year (please specify number of hospitalisations)				
Average length of hospital stay, if any, in ICU (days)				
Average length of hospital stay on a general ward (days)				
% of hospitalised patients admitted through A&E				
Number of follow up visits to a specialist due to the hospitalisation				
Number of follow up visits to a GP due to the hospitalisation				
Number of follow up visits to a nurse due to the hospitalisation				

* BSC = Best Supportive Care

Are there any additional tests or procedures perfomed in addition to any routine follow ups, at the time of disease progression?

RESOURCE USE ASSOCIATED WITH ADVERSE EVENTS DUE TO HCC ACTIVE TREATMENT

We would now like to find out about how certain adverse events associated with sorafenib are treated, irrespective of their incidence. Please indicate how you would manage the following adverse events.

Treatment of adverse events associated with HCC therapies

	% of patients with AE who are hospitalised as an inpatient due to AE	Avg. length of hospital stay for AE (days)	% of patients with AE who are treated as outpatients due to that AE	Avg. No. of AE related outpatient specialist visits per patient	Avg. No. of AE related GP visits per patient	Tests/ Procedures performed (please list)	Medications/Treatment (include dose and duration of medications)
Fatigue							
Weight loss							
Diarrhoea							
Nausea/vomiting							
Abdominal pain							
Alopecia							
Rash							
Hand-foot skin reaction							
Hypertension							
Haemorrhagic events							

PERSONAL AND SOCIAL SERVICES

Please consult a member of your multidisciplinary team if you are uncertain about the use of these services.

Other services

Patient severity	Personal and social services required:	% of patients receiving?	Quantity of the service used (in the appropriate unit)	% of services funded by social services
EXAMPLE:	*Day care*	*20%*	*20 days a month*	*100%*
	Home care	*10%*	*Twice a week*	*20%*
Stable patient on sorafenib	Residential care			
	Day care			
	Home care			
	Other (specify)			
Stable patient on BSC	Residential care			
	Day care			
	Home care			
	Other (specify)			
Progressive patient on sorafenib	Residential care			
	Day care			
	Home care			
	Hospice care			
	Other (specify)			
Progressive patient on BSC	Residential care			
	Day care			
	Home care			
	Hospice care			
	Other (specify)			

Thank you for you time and valuable contribution to this study

RESOURCE USE AND UNIT COSTS

Mean (standard deviation)

Table 1: Monthly Physician visits

Medical Contact	First line – no progression with sorafenib	First line – no progression with BSC	First-line treatment continued – post progression with sorafenib	BSC - post progression
1. Oncologist	0.75 (0.50)	0.38 (0.48)	1.00 (0)	0.38 (0.48)
2. Hepatologist	0.17 (0.19)	0.50 (0.58)	0.58 (0.96)	0.50 (0.58)
3. Macmillan Nurse	0.50 (0.58)	0.50 (0.58)	1.00 (1.15)	1.00 (1.15)
4. Gastroenterologist	0.08 (0.17)	0.25 (0.50)	0.13 (0.25)	0
5. Radiologist	0.08 (0.17)	0	0	0
6. Clinical Nurse Specialist	0.50 (0.58)	0.13 (0.25)	0.50 (0.58)	0.25 (0.50)
7. Palliative Care Physician / Nurse	0.13 (0.25)	0	1.00 (2.00)	0.75 (0.96)

Table 2: Monthly laboratory tests

	First line – no progression with sorafenib		First line – no progression with BSC		First-line treatment continued – post progression with sorafenib		BSC - post progression	
Laboratory Test	**Mean proportion of patients utilising**	**Mean # of tests**	**Mean proportion of patients utilising**	**Mean # of tests**	**Mean proportion of patients utilising**	**Mean # of tests**	**Mean proportion of patients utilising**	**Mean # of tests**
1. AFP test	0.75 (0.50)	0.83 (0.29)	0.75 (0.50)	0.83 (0.29)	0.38 (0.48)	1.00 (0)	0.38 (0.48)	1.00 (0)
2. Liver function test	0.50 (0.58)	0.67 (0.47)	0.50 (0.58)	0.67 (0.47)	0.25 (0.50)	1.00 (0)	0.25 (0.50)	1.00 (0)
3. INR	0.50 (0.58)	0.67 (0.47)	0.50 (0.58)	0.67 (0.47)	0	0	0	0
4. Complete blood count	0.75 (0.50)	1.00 (0)	0.75 (0.50)	1.00 (0)	0.50 (0.58)	1.00 (0)	0.50 (0.58)	1.00 (0)
5. Biochemistry	0.50 (0.58)	1.00 (0)	0.50 (0.58)	1.00 (0)	0.25 (0.50)	1.00 (0)	0.25 (0.50)	1.00 (0)
Other								
1. Endoscopy	0.25 (0.50)	0.33 (0)	0.25 (0.50)	0.33 (0)	0	0	0	0

Table 3: Monthly radiological tests

	First line – no progression with sorafenib		First line – no progression with BSC		First-line treatment continued – post progression with sorafenib		BSC - post progression	
Radiological tests	**Mean proportion of patients utilising**	**Mean # of tests**	**Mean proportion of patients utilising**	**Mean # of tests**	**Mean proportion of patients utilising**	**Mean # of tests**	**Mean proportion of patients utilising**	**Mean # of tests**
1. CT scan (abdominal)	0.73 (0.49)	0.33 (0)	0.73 (0.49)	0.33 (0)	0.73 (0.49)	0.39 (0.10)	0.73 (0.49)	0.39 (0.10)
2. MRI scan (abdominal)	0.28 (0.49)	0.33 (0)	0.28 (0.49)	0.33 (0)	0.28 (0.49)	0.50 (0)	0.28 (0.49)	0.50 (0)

Table 4: Monthly hospitalisation

Hospitalisation	**First line – no progression with sorafenib**	**First line – no progression with BSC**	**First-line treatment continued – post progression with sorafenib**	**BSC - post progression**
Proportion of patients requiring hosp	0.46 (0.31)	0.39 (0.35)	0.42 (0.32)	0.48 (0.30)
Number of hospitalisations	0.16 (0.10)	0.16 (0.10)	0.32 (0.21)	0.40 (0.32)
General ward stay (days)	2.5 (2.89)	7.00 (0)	5.50 (4.20)	5.67 (5.13)
Proportion of A&E admissions	0.11 (0.16)	0.18 (0.18)	0.14 (0.15)	0.35 (0.15)

Table 5: Monthly social care

Social Care	First line – no progression with sorafenib			First line – no progression with BSC			First-line treatment continued – post progression with sorafenib			BSC - post progression		
	Proportion utilising	Mean days	Proportion funded by NHS	Proportion utilising	Mean days	Proportion funded by NHS	Proportion utilising	Mean days	Proportion funded by NHS	Proportion utilising	Mean days	Proportion funded by NHS
1. Residential care	0.02 (0.04)	0	0	0.00	0.00	0.00	0.03 (0.06)	0	0	0.03 (0.05)	6.43 (0)	1.00 (0)
2. Day care	0.02 (0.04)	0	0	0.00	0.00	0.00	0.03 (0.06)	0	0	0.23 (0.26)	5.36 (1.51)	0.00
3. Home care	0.07 (0.05)	4.00 (0)	0.50 (0)	0.09 (0.10)	12.86 (0)	1.00 (0)	0.27 (0.25)	4.00 (0)	0.50 (0)	0.28 (0.10)	12.86 (8.57)	1.00 (0)
4. Hospice	NA	NA	NA	0.09 (0.10)	6.47 (0.05)	0.15 (0.21)	0.10 (0.10)	1.00 (0)	0.50 (0.71)	0.18 (0.10)	14.00 (3.50)	0.43 (0.51)

Table 6: Monthly follow-up associated with hospitalisation

Follow-up visit	First line – no progression with sorafenib	First line – no progression with BSC	First-line treatment continued – post progression with sorafenib	BSC - post progression
1. Specialist	0.25 (0.50)	1.00 (1.41)	0.67 (0.58)	3.00 (0)
2. GP	1.50 (2.38)	0.67 (1.15)	0.50 (0.58)	1.50 (2.12)
3. Nurse	1.75 (2.36)	2.00 (2.83)	1.00 (1.00)	2.00 (2.83)

Table 7: Unit costs for medical staff visits

Resource use item	Unit	Mean unit cost (£)	Mean unit cost (2008 £)	Source	
Oncologist	per contact	151.00	156.04	NHS National Schedule of Reference Costs 2006-07	Consultant Led First Attendance Outpatient Face to Face (TCLFASFF); specialty code 800; Clinical Oncology (attendance without treatment) Total Attendances; LQ £71; UQ £243
Hepatologist	per contact	191.00	197.38	NHS National Schedule of Reference Costs 2006-07	Consultant Led First Attendance Outpatient Face to Face (TCLFASFF); specialty code 306; Hepatology Total Attendances; LQ £150; UQ £251
Specialist Nurse	per hour	30.00	31.00	PSSRU 2007	Schema 9.4 Nurse specialist (Community); costs including qualifications
GP	per consultation	34.00	35.14	PSSRU 2007	Schema 9.8b General practionner, per surgery consultation lasting 11.7 min; costs including qualifications
District Nurse	per hour	30.00	31.00	PSSRU 2007	Schema 9.1 Community nurse (district nurse); costs including qualifications
Palliative care team (1 consultant, 4 nurses, 1 social worker)	per contact	124.00	128.14	NHS National Schedule of Reference Costs 2006-07	Consultant Led First Attendance Outpatient Face to Face (TCLFASFF); speciality code 191;Pain Management Total Attendances ; LQ £202; UQ £255
Specialist visit	per half hour	87.50	90.42	PSSRU 2007	schema 14.4 Consultant: medical, per contract hour; costs including qualifications
Dietician	per contact	32.00	33.07	PSSRU 2007	Schema 12.4 Dietician; costs including qualifications

Table 8: Unit costs for laboratory and radiology tests

Resource use item	Mean unit cost per test (£)	Mean unit cost per test(2008 £)	Source
Laboratory tests			
AFP test	7.12	7.36	Newcastle Upon Tyne Hospitals NHS Trust Diagnostic Services Tariff 2006/2007
Liver Function test	5.90	6.10	Meavy Clinic Tariff Charges April 2006-March 2007
INR	3.84	3.97	Newcastle Upon Tyne Hospitals NHS Trust Diagnostic Services Tariff 2006/2007
Complete blood count	2.29	2.37	Newcastle Upon Tyne Hospitals NHS Trust Diagnostic Services Tariff 2006/2007 (Haematology Laboratory Services - Full blood count)
Complete metabolic panel	96.40	99.62	Newcastle Upon Tyne Hospitals NHS Trust Diagnostic Services Tariff 2006/2007
Radiological tests			
CT scan: abdominal	156.00	161.21	Newcastle Upon Tyne Hospitals NHS Trust Diagnostic Services Tariff 2006/2007
MRI: abdominal	230.00	237.68	Newcastle Upon Tyne Hospitals NHS Trust Diagnostic Services Tariff 2006/2007
Ultrasound: abdominal	96.00	99.21	Newcastle Upon Tyne Hospitals NHS Trust Diagnostic Services Tariff 2006/2007

Table 9: Unit costs for hospitalizations and social care

Resource use item	Unit	Mean unit cost (£)	Mean unit cost (2008 £)	Source
ICU	day	1410.00	1457.08	NHS National Schedule of Reference Costs 2006-07
General Ward	day	323.00	357.20	CIFPA 2004-2005
A&E Admission	admission	90.00	93.00	NHS National Schedule of Reference Costs 2006-07
Residential Care	per day	99.00		Marillac, nursing home,2006
Day Care	per day	130.00	105.58	NHS National Schedule of Reference Costs 2006-07
Home Care	per day	74.00	134.34	NHS National Schedule of Reference Costs 2006-07
Hospice	per episode	84.00	76.47	NHS National Schedule of Reference Costs 2005-06

Table 10: Unit costs for other tests

Resource use item	Mean unit cost per test (£)	Mean unit cost per test(2008 £)	Source
Microbiological examination	23.33	24.11	UCL lab tariff 2007
IV rehydration	2.10	2.10	BNF, 2008
Urea and electrolytes (blood urea nitrogen)	5.90	6.10	Meavy Clinic Tariff Charges April 2006-March 2007
Urea and electrolytes (urine)	23.00	23.00	Mullhaven Medical Laboratory 2008
Endoscopy	750.00	775.04	GI Endoscopy. Meavy Clinic Tariff Charges April 2006-March 2007

Table 11: Unit costs for medications

Medication	Mean drug cost, package price (£)	Source
1. Ferrous sulphate (200mg)	2.10	BNF 2008
2. Dexamethasone	3.27	BNF 2008
3. Loperaminde	0.61	BNF 2008
4 Codeine	0.97	BNF 2008
5. Cyclizine	1.48	BNF 2008
6. Metoclopramide	0.44	BNF 2008
8. Domperidone	1.36	BNF 2008
9. Paracetamol	0.17	BNF 2008
10. Cholestyramine	17.28	BNF 2008
11. Atenolol	0.30	BNF 2008
12. Morphine sulfate	1.87	BNF 2008

Table 12: Adverse events

FATIGUE	
Medical visits	**Mean**
Proportion hospitalized	0.00
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.33 (0.39)
Number of specialist visits	0.75 (0.96)
Number of GP visits	0.25 (0.50)
Routine tests	
Full blood count	1.00 (0)
Liver function test	0.00
Medications (steroids)	
Dexamethoasone mg	4.00
Dexamethasone - dose per day	0.06
Dexamethasone - duration per month	30.00
Dietician referral	0.00

WEIGHT LOSS	
Proportion hospitalized	0.00
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.25 (0.30)
Number of specialist visits	1.00 (1.15)
Number of GP visits	0.00
Routine tests	
Full blood count	0.00
Urea and electrolytes	0.00
Liver function test	0.00
Medications (steriods)	
Dexamethasone - dose mg	4.00
Dexamethasone - dose per day	0.06
Dexamethasone - duration per month	18.90
Dietician referral	0.00
DIAHORREA	
Proportion hospitalized	0.01 (0.03)
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.33 (0.26)
Number of specialist visits	1.50 (0.58)
Number of GP visits	0.25 (0.50)
Routine tests	
Full blood count	0.00
Liver function test	0.00
Other	
Microbiological exam (stool test)	1.00
IV rehydration	0.25
Medications	
Loperamide-dose mg	2.00
Loperamide- dose per day	3.50
Loperamide -duration per month	30.00
Codeine - dose mg	30

Codeine - dose per day	3
Codeine -duration per month	1
NAUSEA/VOMITTING	
Proportion hospitalized	0.00
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.23 (0.33)
Number of specialist visits	1.00 (1.15)
Number of GP visits	0.00
Medications (anti-emetics)	
Metoclopramide-dose	10.00
Metoclopramide- dose per day	4.00
Metoclopramide- duration per month	15.00
ABDOMINAL PAIN	
Proportion hospitalized	0.00
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.03 (0.03)
Number of specialist visits	1.00 (1.15)
Number of GP visits	0.00
Routine tests	
Full blood count	0.00
Urea and electrolytes	0.00
Liver function test	0.00
Other tests	
Abdominal X Ray	0.33 (0.58)
Ultrasound	0.00
CT Scan	0.33 (0.58)
Medications (pain killers)	
Oromorph – dose mg	10.00 (0)
Oromorph – duration per month	30.00 (0)
ALOPECIA	
Proportion hospitalized	0.00
Average hospital stay (non ICU, days)	0.00

Proportion treated as outpatients	0.03 (0.03)
Number of specialist visits	1.00 (1.15)
Number of GP visits	0.00
RASH	
Proportion hospitalized	0.00
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.28 (0.25)
Number of specialist visits	1.25 (0.96)
Number of GP visits	0.00
Routine tests	
Full blood count	0.00
Urea and electrolytes	0.00
Liver function test	0.00
HAND-FOOT SKIN REACTION	
Proportion hospitalized	0.01 (0.03)
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.33 (0.26)
Number of specialist visits	1.25 (0.96)
Number of GP visits	0.00
Routine tests	
Full blood count	0.00
Urea and electrolytes	0.00
Liver function test	0.00
HYPERTENSION	
Proportion hospitalized	0.00
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.25 (0.31)
Number of specialist visits	1.50 (1.00)
Number of GP visits	0.75 (0.96)
Tests/procedures	0.00
Treatments – Atenolol mg	50.00
Atenolol – dose per day	1.00

Atenolol – duration per month	30.00
HAEMORRHAGIC EVENTS	
Proportion hospitalized	0.01 (0.01)
Average hospital stay (non ICU, days)	0.00
Proportion treated as outpatients	0.03 (0.05)
Number of specialist visits	1.00 (1.15)
Number of GP visits	0.00
Endoscopy	1.00 (0)