Bayer Healthcare response to ACD - Sorafenib for advanced hepatocellular carcinoma.

Summary

Patients with advanced HCC (hepatocellular carcinoma) have a high unmet clinical need and limited treatment options available.[1] Sorafenib is the only treatment to have demonstrated a survival benefit in advanced HCC for over 30 years and more than 75 placebo controlled trials.[2 3]

The Appraisal Committee concluded that sorafenib, as a treatment for HCC in patients for whom surgical or locoregional therapy has failed or is unsuitable, would not be a cost effective use of NHS resources.[4] It is anticipated that there will be around 600 patients in England and Wales eligible for sorafenib.[5]

Cost effectiveness, as measured by the cost per QALY, is only one factor to consider. Estimates of cost effectiveness do not take into account the poor prognosis and high 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 carers. In addition the majority of these patients have underlying liver disease as well as advanced HCC compromising their ability to show benefit from treatment and so creating an inequity in ability to access treatment. Patients suffering from rare diseases such as advanced HCC should have equal opportunities to health and recommendations should reflect societal preferences for life extending medicines and reflect NICE's commitment to supporting NHS innovation.

The current guidance fails to outline how the appraisal committee has considered patient and societal preferences for life extending medicines, equal opportunities to health for patients with underlying disease and suffering from rare diseases that disproportionately affect certain population groups, NICE's commitment to innovation and the Government commitment to Improving Outcomes for Cancer patients.

The preliminary recommendations, if implemented without amendment, will leave no treatment options for the small number of patients with advanced HCC, where surgical or locoregional therapies have failed or are not suitable.

Consideration and interpretation of relevant evidence:

The Appraisal Committee concluded that sorafenib as a treatment for HCC in patients for whom surgical or locoregional therapy has failed or is unsuitable would not be a cost effective use of NHS resources.

The appraisal committee raised concerns regarding the uncertainty of the cost effectiveness estimate given alternative methods of extrapolating the survival data. The base case uses a lognormal distribution, which provided the best fit for the SHARP data. An alternative model was proposed which used the Weibull distribution. However an exploratory analysis of published long-term survival of patients with HCC showed that the lognormal distribution consistently provides a better fit than the Weibull distribution for overall survival in HCC. Based on these published data the lognormal distribution has shown consistently the best fit in all patient groups than the Weibull distribution. (Further details of this analysis can be found in table 1).

Paragraphs 3.14, 3.18 and 3.22 in the appraisal consultation document suggest that the adverse events rates used in the model were estimated from expert clinical opinion. It should be noted that the rate of adverse events was taken from the SHARP study and the resource use for treating such events was obtained from clinical expert opinion.

Paragraph 4.11 reports the survival gains observed in the clinical study and the economic model. It should be noted that the 2.8 months survival gain observed in the clinical study was based on median overall survival whilst the 6.1 months observed in the economic model was based on

mean overall survival, which reflects the survival gains for patients who were censored at the end of the clinical study period.

Suitability of the provisional recommendations of the appraisal committee as a sound and suitable basis for the preparation of guidance to the NHS

The preliminary recommendations, if implemented without amendment, will leave no treatment options for patients with advanced HCC, where surgical or locoregional therapies have failed or are not suitable. Without such treatments these patients will die within 8 months.

Patients with HCC present with advanced disease and limited treatment options mean these patients have a very poor prognosis with 5 year survival rates of <5%. Sorafenib is the only systemic treatment that has been shown to significantly improve overall survival in advanced HCC, with a 44% increase compared to placebo. Furthermore sorafenib is the only treatment to have demonstrated a survival benefit in advanced HCC for over 30 years. No systemic agent has shown a survival benefit versus placebo in more than 75 randomised controlled trials. The provisional recommendation does not take into account the high unmet clinical need of this small group of patients and is therefore not a sound and suitable basis for the preparation of guidance to the NHS.

There are approximately 2000 new cases of HCC diagnosed in England and Wales each year.[6] Of these the population eligible for sorafenib is around 600.

Ensuring equalities in health and reflecting societal values

NICE accepted that sorafenib should be appraised under the End of Life criteria. These criteria were introduced to ensure access to life extending medicines for patients with a short life expectancy, where small numbers of patients are affected. It is disappointing that the recommendations for sorafenib do not reflect the preferences of the public and policy makers to extend survival for the small number of patients with this poor prognosis disease.

Equality

Prevalence of HCC is high in patients from black and minority ethnic migrant groups.
There are striking variations in health status, prevalence of diseases and health behaviours amongst ethnic groups in the population. These inequalities relate to variations in disease prevalence, differential access to services, differential delivery and take up of services and differential exposure to risk factors.[7] These groups may have limited access to the NHS and therefore present with a more advanced stage of the disease, thereby making them ineligible for treatments such as surgical or locoregional intervention. Implementation of the recommendation for sorafenib, without amendment will mean these patients have no treatment options available to them thereby generating inequalities in health outcomes.

The NICE citizen's Council concluded that where feasible, NICE should support strategies to improve the health of the population while offering particular benefit to the most disadvantaged so as to reduce health inequalities.[8] Furthermore patients suffering from rare diseases should have equal opportunities to health.

The majority of patients who develop advanced HCC have underlying diseases and therefore lower existing quality of life compared to the general population. This lower quality of life compromises their ability to show benefit from treatment for advanced HCC. This inability to show the magnitude of gain in quality of life experienced by the general population creates an inequity in the ability of demonstrate the same cost effectiveness ratios for a given treatment and therefore results in an inequitable ability to access treatment.

NICE is committed to promoting equality and eliminating unlawful discrimination. The current guidance fails to show how NICE have given these equality issues detailed consideration.

Sorafenib is an orphan drug and the only treatment to have demonstrated a survival benefit in patients with advanced HCC. These patients have no other treatment options and therefore particular consideration should be given to ensuring health equality in this orphan disease with an exceptionally poor prognosis.

Cancer survival rates in the UK are already one of the worst in Europe.[9] This may be due to later diagnosis and the availability of radiotherapy and drug treatments. HCC is often diagnosed at a late stage when patients have limited treatment options with clinical benefit available to them. The preliminary recommendations for sorafenib, if implemented without amendment do not reflect the Governments commitment to improving outcomes in cancer patients and inequalities in UK cancer treatment will prevail.

NICE's commitment to innovation

The development and commercialisation of orphan drugs are associated with incentives to encourage manufacturers to develop and market treatments for rare diseases.[10] This initiative helps to give patients suffering from rare diseases access to the same quality of treatment as other patients.

With the increasing importance of demonstrating product value through cost effectiveness, incentives to develop and commercialise drugs to treat orphan diseases should extend beyond regulatory and exclusivity incentives to cover health technology assessment to ensure equality of access to treatment for patients suffering from rare diseases.

NICE states the End of Life policy takes into account NICE's responsibility to recognise the benefits to the NHS of innovation and supporting the development of innovative treatments that are anticipated to be licensed for small groups of patients who have an incurable illness.[11]

The current recommendation fails to support NICE's commitment to innovation. The recommendation is inconsistent with current clinical guidelines that recommend sorafenib as standard therapy for patients with advanced HCC for whom no curative option is available.[12] Prior to the availability of sorafenib guidelines[13] stated 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. Failure to recommend sorafenib in this indication will undoubtedly have a significant effect on future clinical research in this area, particularly as no other systemic agent has shown a survival benefit versus placebo in more than 75 randomised controlled trials.

References

[1] American Cancer Society website. Liver Cancer – Detailed Guide. http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=25 Accessed May 2009.

[2] Llovet JM, Ricci S, Mazzaferro V, Hillgared P, Gane E, Blanc JF. et al. Sorafenib In advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul 24; 359(4): 378-90.

[3] Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma - an updated analysis of randomized controlled trials. Alimentary Pharmacology & Therapeutics 2006;23:1535-47.

[4] National Institute for Health and Clinical Excellence. Sorafenib for advanced hepatocellular carcinoma – appraisal consultation document. www.nice.org.uk Accessed: May 2009.

[5] Bayer plc. Data on File: BayerSchering HCC Advisory Board (October 2007). 2007.

[6] http://info.cancerresearchuk.org/cancerstats/types/liver/incidence/ Accessed 11th November 2008.

[7] National Institute for Health & Clinical Excellence. NICE's equality scheme and action plan 2007-2010. www.nice.org.uk Accessed: May 2009.

[8] National Institute for Health and Clinical Excellence. Social Value Judgements. Principles for the development of NICE guidance. . www.nice.org.uk Accessed: May 2009.

[9] Berinno F, De Angelis R, Stant M et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. Lancet Oncol 2007: 8: 773–783.

[10] Orphan medicinal product designation in the European Union. European Medicines Agency. http://www.emea.europa.eu/htms/human/orphans/intro.htm. Accessed March 2007

[11] National Institute for Health & Clinical Excellence. Appraising life extending, end of life medicines. www.nice.org.uk Accessed: May 2009.

[12] Personal communication

[13] Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003 May; 52 Suppl 3:iii1-iii8.

Appendix 1: Analysis of long-term overall survival data of HCC patients – using published Kaplan-Meier curves (An exploratory analysis)

Background and objective

The National Cancer Institute NSW has prepared a report on survival estimates for patients with hepatocellular carcinoma (HCC) by extent of disease at diagnosis (NCI 2007, IARC 1995). Kaplan-Meier curves for local, regional, distant and unknown HCC were estimated, together with overall survival estimates for two periods of interest: cases diagnosed 1999-2004 and cases diagnosed 1972-2004 (NCI 2007).

As the only source of long-term survival in HCC, these analyses provide useful information in the health economic modeling of the disease.

Thus a preliminary analysis was conducted based on the Kaplan-Meier curves of the report to determine which statistical survival distribution best fits the long-term overall survival of patients diagnosed with HCC.

Methodology

Data manipulation

Data from the published Kaplan – Meier curves (NCI 2007) were read using an internally developed graph analyzer tool, based on MS Excel. As no information on the absolute patient cohort was available from the report, hypothetical patient cohorts were created with 100,000 patients in each.

From the values of the Kaplan-Meier curves, the number of failures at several time points was calculated. No information on the number of patients lost to follow up was available, therefore the difference between the number of patients at risk at subsequent time periods were assumed to be due to failure (death). Each time point where failures occurred was assigned as the time to death of those patients who failed at that time point. At the last point of observation all remaining patients were assumed to be censored.

This restructuring of the dataset was carried out in the statistical software STATA 10 SE, and was analyzed with standard survival analysis techniques.

Survival analysis

The following statistical survival distributions were fitted to the transformed data:

- exponential,
- Weibull,
- lognormal,
- log-logistic,
- gamma, and
- Gompertz.

The above statistical models are distinguished by the shapes of the hazard functions. While the underlying hazard of exponential model is constant, the Weibull and Gompertz is monotonic, the lognormal and log-logistic can capture non-monotonic hazard as well. If it is believed that the hazard rate is likely to increase and then decrease, or increase followed by leveling off then choosing a monotonic hazard rate cannot be justified.

Goodness of fit was assessed based on formal statistical criteria. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to determine the best fitting shape. The lowest value of the AIC and BIC indicates the best fit with the empirical data.

Results

From the above listed distributions, each was fitted to the empirical Kaplan-Meier curves. With the exception of the gamma distribution, estimated coefficients and goodness of fit measures could be retrieved for each of the distributions. The likelihood function of the gamma distribution did not converge (due to the low variation of event times); therefore results for this distribution could not be reported.

The results were consistent across patient groups. The lognormal and log-logistic distributions gave the best fit, based on both the AIC and BIC (see tables Table 1 - Table 4).

The economic model of the SHARP data uses the lognormal distribution; however the Weibull distribution was suggested as a potential alternative. This document focuses on comparing the appropriateness of the lognormal model to the Weibull model.

Graphically, Figure 1- Figure 4 shows the difference in fit between the Weibull and lognormal distributions. The lognormal distribution fits the beginning of the Kaplan-Meier curve better. Since this part of the curve has the most patients at risk, and thus the most information, this fit transfers into an advantage in statistical fit as well.

Table 1 Model fit, patients with unknown HCC

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exp	100000	-238948.4	-238948.4	1	477898.9	477908.4
weib	100000	-201754.3	-201754.3	2	403512.7	403531.7
ln	**100000**	**.**	**-179924.4**	**2**	**359852.8**	**359871.8**
logl	**100000**	**.**	**-177453.9**	**2**	**354911.8**	**354930.8**
gom	100000	.	-180883.7	2	361771.4	361790.5

Figure 1 Kaplan Meier and fitted survival curves – patients with unknown HCC

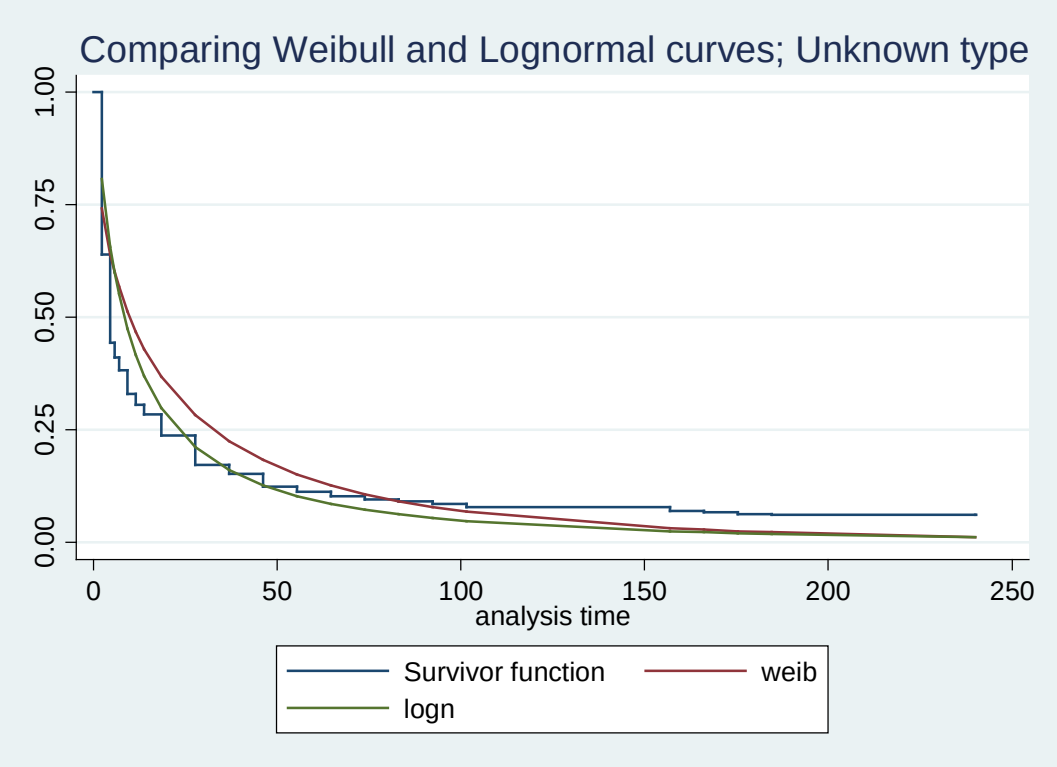


Table 2 Model fit, patients with local HCC

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exp	99900	-256520.6	-256520.6	1	513043.2	513052.7
weib	99900	-210527.1	-210527.1	2	421058.2	421077.2
ln	**99900**	**.**	**-193127**	**2**	**386258**	**386277**
logl	**99900**	**.**	**-193208.1**	**2**	**386420.1**	**386439.2**
gom	99900	.	-200812.3	2	401628.7	401647.7

Figure 2 Kaplan Meier and fitted survival curves – patients with local HCC

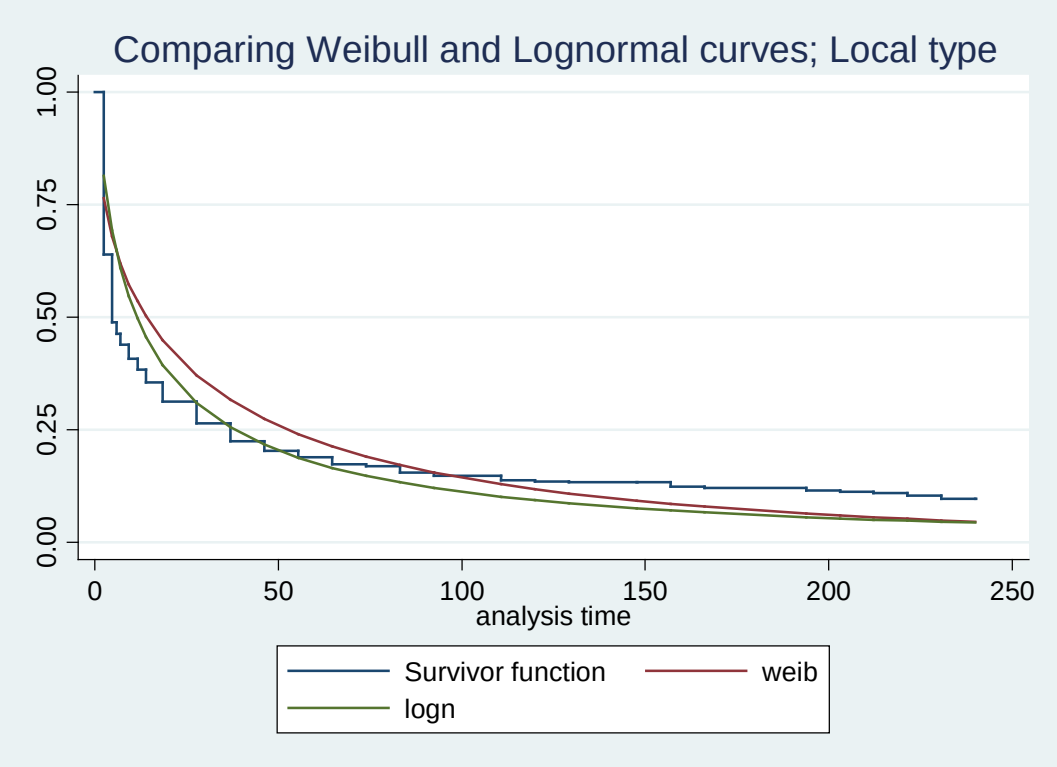


Table 3 Kaplan Meier and fitted survival curves – patients with regional HCC

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exp	100000	-230501	-230501	1	461004	461013.5
weib	100000	-195538.7	-195538.7	2	391081.5	391100.5
ln	**100000**	**.**	**-168986.2**	**2**	**337976.4**	**337995.4**
logl	**100000**	**.**	**-163648.1**	**2**	**327300.1**	**327319.2**
gom	100000	.	-172905.4	2	345814.9	345833.9

Figure 3 Kaplan Meier and fitted survival curves – patients with regional HCC

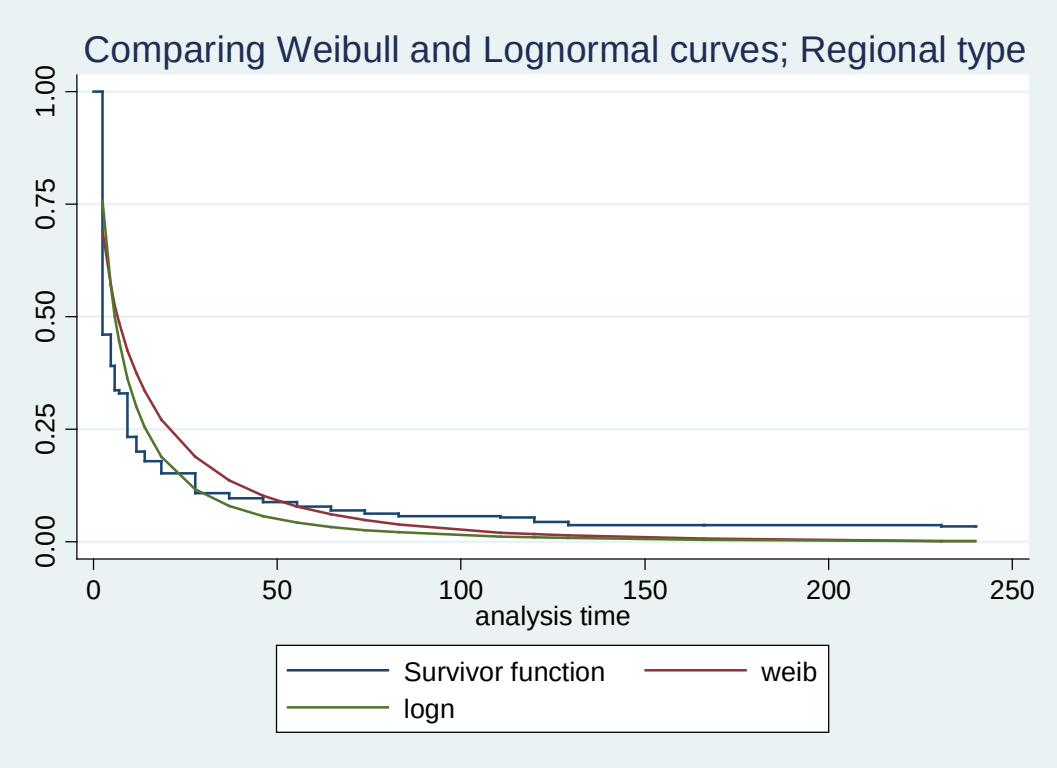
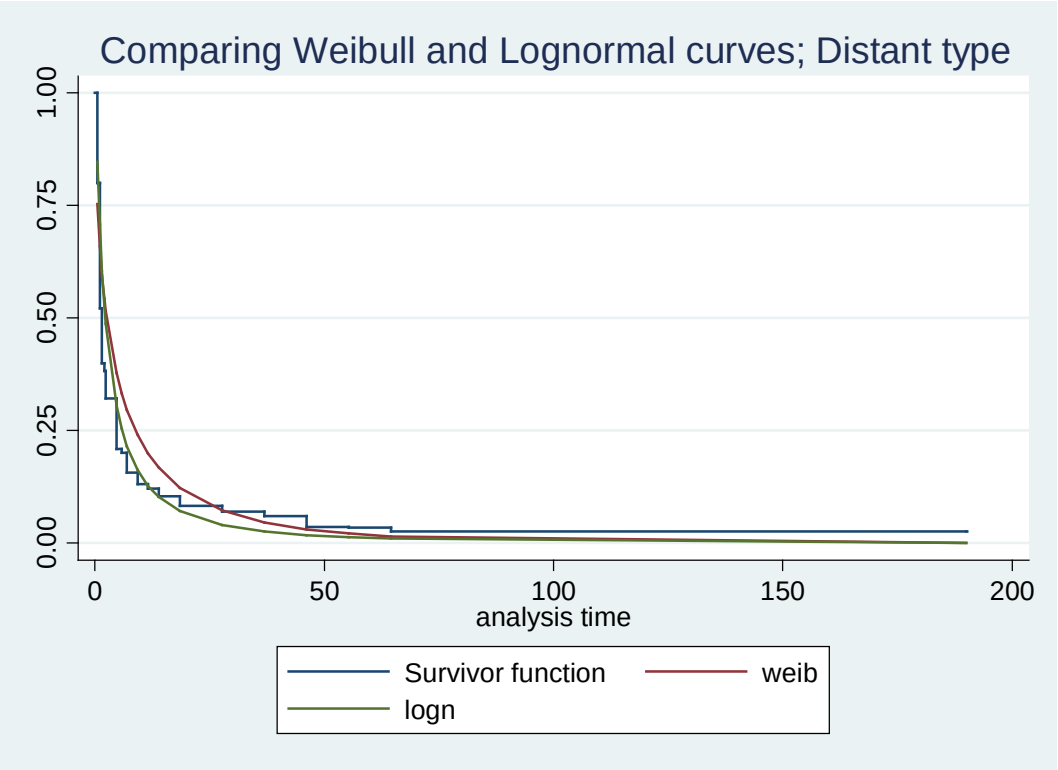


Table 4 Kaplan Meier and fitted survival curves – patients with distant HCC

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exp	100000	-259533.9	-259533.9	1	519069.9	519079.4
weib	100000	-204448.2	-204448.2	2	408900.3	408919.4
ln	100000	.	-178858.3	2	**357720.6**	357739.6
logl	100000	.	-174688.4	2	**349380.8**	349399.8
gom	100000	.	-182457.8	2	364919.5	364938.6

Figure 4 Kaplan Meier and fitted survival curves – patients with regional HCC



Discussion

Exploratory analysis of published long-term survival of patients with HCC showed that the lognormal distribution consistently provides a better fit than the Weibull distribution for overall survival in HCC. The lognormal distribution has shown consistently the best fit in all patient groups compared to the Weibull distribution. The results from the long-term analysis suggest that the lognormal distribution would provide a better fit then Weibull distribution, thereby reducing uncertainty in extrapolation estimates.

Similar results were found in breast cancer and ovarian cancer patients by Royston (2001). When separating patient groups by prognostic scores, he found a significant non-monotonicity of the hazards, suggesting the use of distributions that can accommodate non-proportional hazard. By assessing the fits of different parametric survival distribution, gamma and lognormal provided the best fit in breast cancer, while log-logistic and lognormal proved to be the best fit in ovarian cancer.

References

Report from the National Cancer Institute NSW (NCI). DOH qtr Sep-07; MERU Reference: 08-006.

International Agency for Research on Cancer (IARC), World Health Organization, International Association of Cancer Registries. Chapter 4 - Coding. In: Esteban D, Whelan S, Laudico A, Parkin D, eds. Manual for Cancer Registry Personnel: IARC Technical Report No 10. Lyon: International Agency for Research on Cancer 1995:p 4.32.

Royston P. The lognormal distribution as a model for survival time in cancer, with an emphasis on prognostic factors. Statistica Neerlandica. 2001; 55: 89-104.

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11/05/09

L Woodward
National Institute for
Health and Clinical Excellence
Level 1A, City Tower
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Manchester
M1 4BD

Dear Ms Woodward

Thank you for the opportunity to comment on the ACD for Sorafenib in HCC on behalf of the NCRI and RCP. We are disappointed that NICE feel that the case cannot be supported on cost effectiveness grounds. As a point of presentation we feel that this should be stated in the summary, which as it currently reads, does not detail the robust clinical case and that it is the cost effectiveness that brought about the final decision.

We would like to emphasise the absence of a realistic alternative treatment for HCC. The inevitable consequence of this decision, as oncologists have experienced following prior NICE decisions, is a prolonged uneasy period of patient and doctor unhappiness and difficult consultations where the *de facto* responsibility for a NICE decision is placed with the oncologist. A response to this clinical reality would be appreciated.

Yours sincerely

John Bridgewater
Senior Lecturer in Medical Oncology

For the attention of Laura Malone
Technology Appraisal Programme Manager
By email: Laura.Malone@nice.org.uk

27 May 2009

British Liver Trust response to the sorafenib ACD

Thank you for the opportunity to comment on the appraisal consultation document relating to the use of sorafenib for advanced hepatocellular carcinoma. The British Liver Trust notes with dismay and concern the negative guidance regarding use of this technology. We write to dispute the conclusion that sorafenib would not be "an effective use of NHS resources".

i) Do you consider that all of the relevant evidence has been taken into account?

No. We feel that insufficient attention was given to the evidence of the value to patients of treatment contained in the submissions of the Rarer Cancers Forum and others. We would also urge NICE to give more consideration to the value to patients of treatment options.

Many patients live with the risk of HCC, knowing they have cirrhosis. They live with uncertainty, hopelessness and often stigma and isolation due to the image of liver disease. When patients are diagnosed with HCC, they often experience depression from the poor prognosis and a range of symptoms including severe pain that cannot be treated without worsening their liver condition.

Other symptoms include ascites, fluid in the abdomen that can press on the stomach making it difficult to eat and even to breathe. Hepatic encephalopathy can make everyday functions including conversation, writing and staying awake difficult.

Only a very few patients are offered curative treatment, and even then, many live with the uncertainty about whether they will receive a liver transplant before the tumour spreads, or whether they will die as a complication of surgery (liver resection has a relatively high mortality rate).

Patients with HCC are often many years younger than those with other cancers, and extra time is of particular importance to people who may have young families and working lives to put in order before death. For both those

patients with HCC and those who know they are at risk of developing it, we urge a decision that takes away the uncertainty of accessing effective treatment and reaffirms that there is value in treating patients with a stigmatised condition.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

The Trust feels that the preliminary views on the resource impact and implications for the NHS are not appropriate, because the overall cost to the NHS would be small. The evidence submitted to NICE assumed that 700 patients each year would need to be treated. The Trust has heard evidence from Dr Paul Ross of King's College Hospital that the actual number could be much smaller, perhaps as few as 200 patients, if patients were given more appropriate and effective treatment earlier in their disease pathway including chemo-embolisation.

Even with as many as 700 patients, this is a small number that should make sorafenib considered an orphan drug and treated with special consideration for the small numbers involved. The cost impact on the NHS should be considered in the light of the whole disease rather than the cost per QALY for individual patients.

The cost to the NHS's reputation of determining that patients with one particular type of advanced cancer should be denied the only effective life-extending treatment should also be considered.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

We believe that it is perverse to recommend that sorafenib is clinically effective and meets the new supplementary criteria on end-of-life care but should not be used on affordability grounds. Patients were led to believe that the new supplementary advice to the Appraisal Committee on end-of-life care would give compassionate treatment through relaxing the stricter cost per QALY thresholds normally used by NICE. This supplementary advice is relatively new and this appraisal is therefore one of its first significant tests. The Appraisal Committee stated that sorafenib met the criteria to be considered under this advice. However, we do not believe that the decision on the effective use of available resources adequately adheres to the advice. It should be noted that the advice was intended to be "robust for the long term and to achieve its intended purpose", and a refusal to recommend sorafenib despite its clinical effectiveness does not achieve this.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

In many other cancers, there are several life-extending chemotherapy treatments available, and it may be appropriate to consider whether new medicines are effective. This is not the case in liver cancer. It is therefore inappropriate to consider the use of sorafenib for liver cancer as an ineffective use of available resources compared with other treatments for other cancers, rather than comparing it against no treatment for this group of patients.

There is a strong case for compassionate treatment for HCC patients with sorafenib based on the patient experience of effective NHS care. The patient population for this NICE appraisal have already suffered setbacks earlier in the patient pathway, many of which could have been addressed by NHS resources. We would like to see more effective use of NHS resources in prevention, including in hepatitis B vaccination; early identification of people with cirrhosis; addressing delays and inadequacies in treatment of hepatitis B, hepatitis C and alcohol use disorders; prompt referral of cirrhotic patients for specialist management; and screening of cirrhotic patients for treatment of HCC with potentially curable tumours. The group of patients who require sorafenib have all failed to benefit from such NHS services, and so should not be denied the only effective intervention left at the NHS's disposal for them.

There is a strong link between liver disease, including liver cancer and health inequalities. These relate to socio-economic status and region for alcohol-based risk factors in particular; and ethnicity and immigration history (from an area of the world where the infections are endemic, including much of Asia and Africa) for hepatitis B and C infection.

In addition to the points above, the Trust is concerned about the impact of the provisional recommendations in deterring future innovation in the treatment of advanced liver disease and liver cancer. Innovations in the treatment of advanced liver disease, including liver cancer, are desperately needed.

Liver disease is the only one of the top five 'big killers' with significant increases in age-related mortality. Improvements in the management of precursor diseases such as hepatitis B and C infection are likely to increase the number of patients surviving with cirrhosis to develop HCC in the future. This is the only chemotherapeutic drug licensed for this indication. Should this therapy fail to be approved by NICE, it is unlikely there will be UK trials or other developments in this field in the future. This is especially true given the small patient population, which reduces the incentives for pharmaceutical companies to invest in innovations for advanced liver cancer. A negative NICE decision will have a disproportionately negative impact on future treatments for liver cancer.

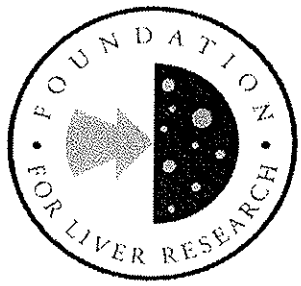
Dear Laura

Thank you for the opportunity to comment on the Appraisal Consultation Document for the above single technology appraisal.

I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.

Many thanks and best wishes

[redacted]
NICE Liaison Team
Department of Health



Laura Malone, Technology Appraisal Project Manager
National Institute for Health & Clinical Excellence

6th May 2009

Dear Ms Malone

Re: Sorafenib for the treatment of advanced hepatocellular carcinoma

In response to your letter seeking of views on the Appraisal Consultation Document I would point out that the patient group being considered, namely those in whom surgical or local/regional therapies have failed or are not suitable, represents a very wide spectrum of hepatocellular cancer. Some of these patients will have biologically highly active tumours or will have developed complications relating to the ablation therapy. In others, further treatment by ablation will not have been proceeded with because of the situation of the tumour in the liver or because liver function was or has become poor over the period of treatment whether or not due to progression of the tumour. A blanket decision such as is recommended also does not take account of what, for hepatologists, has been an extraordinary event, namely that HCC tumour growth can be affected by a chemotherapeutic agent based on a multi-kinase inhibitor action. The controlled trials done to date have given essentially similar results though with some differences in benefit time and new trials are being set up all round the world on looking at the value of sorafenib in combination with local/regional therapies in the treatment of early phase disease. This makes considerable sense as it would be in accord with the effects of chemotherapeutic agents in other tumours in terms of the best time at which to achieve a reduction in tumour growth rate.

The decision of the committee appears to be based largely on the expense of the drug when compared with survival benefit as estimated by Fqaly's and incremental F/LYG, with the calculations giving costs above what is acceptable for the use of NHS resources. This may well be so but the committee should be aware that patients with hepatocellular carcinoma are now asking for this treatment in the UK, having learnt of the agent through the internet but also because of its wide use in the USA and in Europe. In practice it would be more helpful for NICE in my view to have come down with a firm recommendation as to a restricted use for the drug based not only on present knowledge but on the expert advice of hepatologists and oncologists currently working in this area.

Yours sincerely

Response from Oxfordshire PCT to ACD Sorafenib for the treatment of advanced hepatocellular carcinoma

We agree with the recommendation in the consultation document not to recommend sorafenib.

Whilst we are mindful of the poor prognosis for this group of patients and the limited treatment options available to them, we would be extremely concerned if a treatment with such a high cost per QALY were recommended to the NHS. We do not feel that the high cost of a treatment which; does not appear to reduce the time to symptomatic progression, even if this may be complicated by the potential side effects of the drug, which has a short median overall survival and short time to radiological disease progression can be justified. The potential benefits do not, for us, outweigh the side effect profile or the costs of the drug where resources could be used elsewhere. Whilst a median overall survival time of 3 months is seen by our consultants as a reasonable expectation we have to take into account the quality of that life for the patients concerned and the fact that paying for one treatment withdraws money from others.

We welcome the consideration which the appraisal committee gave (paragraph 4.13) to the potential benefit to the subgroup of black and minority ethnic patients and note, with regret, the lack of evidence to assess this.

We have considered the suggestion that a single PCT might only expect a few patients to be treated each year and that the overall cost will not, therefore, be very high. However, we would be concerned that to agree to this treatment, even considering it under the end of life advice, would create further precedents for future technologies.

The PCT thanks NICE for the opportunity to comment on the appraisal.

Response to the Appraisal Consultation Document:
Sorafenib for the treatment of advanced hepatocellular carcinoma (HCC)
May 2009

This response is submitted on behalf of
Rarer Cancers Forum
Hepatitis B Foundation UK

We are grateful for the opportunity to comment on this Appraisal Consultation Document but very disappointed in its preliminary recommendations. This is the first new medicine for HCC in thirty years and these patients have a notoriously poor prognosis.

1**. Do you consider that all of the relevant evidence has been taken into account?**
The Appraisal Committee carefully considered the relevant clinical-effectiveness evidence and the testimony from clinical specialists and patient experts, and concluded that sorafenib is a clinically effective treatment for advanced HCC in patients for whom surgical or locoregional therapy has failed or is not suitable.

We welcome the Committee's conclusion that the population and sorafenib meet the criteria for an appraisal of a life-extending, end-of-life treatment, and that the evidence presented is supported by robust data.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?
The bottom line appears to be that this is a clinically effective treatment but is too expensive for the NHS. Could a risk share scheme could be explored with the manufacturer?

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?
No. Sorafenib is the accepted standard of care in the majority of countries in Europe and North America. We would like the Committee to explore the issues of a risk share scheme with the manufacturer. We would also like the Committee to re-consider patients awaiting liver transplantation. Sorafenib may be critical in tiding them over until they can have their surgery and the hope of significantly improved life expectancy.

4. Are there any equality related issues that need special consideration that are not covered in the ACD?
No.

Dear Lynn

The Royal College of Pathologists have not comments to make at this stage of the consultation.

Regards
[redacted]

Dear Lynn/Laura

I write on behalf of [redacted] with relation to the attached response to this ACD from John Bridgewater (the NCRI/RCP/RCR/ACP/JCCO nomination for the clinical expert role for this technology). The nominating organisations listed above hope that NICE will take note of the heartfelt comments within Dr Bridgewater's letter.

Best wishes
[redacted]

[redacted]

[redacted]

[redacted]

11/05/09

L Woodward
National Institute for
Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

Dear Ms Woodward

Thank you for the opportunity to comment on the ACD for Sorafenib in HCC on behalf of the NCRI and RCP. We are disappointed that NICE feel that the case cannot be supported on cost effectiveness grounds. As a point of presentation we feel that this should be stated in the summary, which as it currently reads, does not detail the robust clinical case and that it is the cost effectiveness that brought about the final decision.

We would like to emphasise the absence of a realistic alternative treatment for HCC. The inevitable consequence of this decision, as oncologists have experienced following prior NICE decisions, is a prolonged uneasy period of patient and doctor unhappiness and difficult consultations where the *de facto* responsibility for a NICE decision is placed with the oncologist. A response to this clinical reality would be appreciated.

Yours sincerely

John Bridgewater
Senior Lecturer in Medical Oncology

Good morning Laura

Thank you for giving the Welsh Assembly Government the opportunity to comment on NICE's Appraisal Consultation Document in connection with the above appraisal. We are content with the technical detail of the evidence supporting the appraisal and have no further comments to make at this stage.

Kind regards

[redacted]