NICE National Institute for Health and Care Excellence

NICE guidance

Sorafenib for treating advanced hepatocellular carcinoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA189.

1 Recommendations

1.1 Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment, only if the company provides sorafenib within the agreed commercial access arrangement.

1.2 This recommendation is not intended to affect treatment with sorafenib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

2 The technology

Table 1 Summary of sorafenib

Description of the technology	Sorafenib (Nexavar, Bayer) is a multikinase inhibitor that inhibits tumour blood vessel development and tumour cell proliferation. It does this by inhibiting the Raf cascade, vascular endothelial growth factor and platelet-derived growth factor receptors of tumour cells, vascular endothelial cells and pericytes.
Marketing authorisation	Sorafenib has a marketing authorisation in the UK for treating hepatocellular carcinoma.
Adverse reactions	The summary of product characteristics includes the following conditions that may be associated with sorafenib treatment: dermatological toxicities, hypertension, haemorrhage, cardiac ischaemia and/or infarction, gastrointestinal perforation, hepatic impairment and wound healing complications. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Sorafenib is administered orally as 200-mg film-coated tablets. The recommended dosage is 400 mg twice daily (a total daily dose of 800 mg). The dosage may be adjusted to 2×200-mg tablets once daily if adverse drug reactions are suspected. The summary of product characteristics recommends that treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.
Price	The price for a pack of 200-mg tablets (112 tablets per pack) is £3,575.56. The company agreed a nationally available price reduction for sorafenib with the Commercial Medicines Unit. The pricing agreement considered during guidance development was that the company (Bayer) had agreed a commercial access agreement with NHS England inclusive of the reduction for sorafenib agreed with the Commercial Medicines Unit. The commercial access agreement replaces the Commercial Medicines Unit price used during the Cancer Drugs Fund reconsideration of technology appraisal guidance 189. The details of this commercial access agreement are commercial in confidence.

3 Evidence

3.1 The appraisal committee considered evidence submitted by Bayer and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on sorafenib for treating advanced hepatocellular carcinoma.

3.2 The company's original submission presented clinical effectiveness data from the SHARP study. SHARP was a multicentre, double-blind, placebo-controlled, randomised trial in patients with advanced hepatocellular carcinoma who had not received previous systemic treatment. The study included 602 patients and assessed the effect of sorafenib plus best supportive care (n=299) compared with placebo plus best supportive care (n=303). The primary outcomes in SHARP were overall survival and time to symptomatic progression.

3.3 Sections 4.1 to 4.17 reflect the committee's discussion of the evidence submitted in the original appraisal. Section 4.18 onwards reflects the committee's discussion of the additional evidence submitted for the Cancer Drugs Fund reconsideration, which focused on:

- data from the key source of evidence, SHARP
- observational data from Palmer et al. (2013) and the GIDEON study to validate survival extrapolations from the company's original submission
- estimates of treatment duration using individual patient data for time on treatment from SHARP and GIDEON
- updated resource use data
- cost-effectiveness analyses using a new Commercial Medicines Unit price, providing sorafenib at a reduced cost (commercial in confidence)
- estimates of how much sorafenib is wasted.

3.4 See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence and the history for full details of the evidence used for NICE's original technology appraisal guidance on sorafenib for treating advanced

hepatocellular carcinoma.

4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of sorafenib, having considered evidence on the nature of hepatocellular carcinoma and the value placed on the benefits of sorafenib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.2 The committee considered the UK treatment pathway for patients with hepatocellular carcinoma. The clinical experts described that in UK clinical practice one third of patients with hepatocellular carcinoma would be eligible for procedures such as local resection, radiofrequency ablation or chemoembolisation. They noted that these procedures are not considered clinically effective for approximately 50% of patients, who would progress to further locoregional therapy or systemic treatment. The committee accepted that the scope of this technology appraisal was restricted to these patients. The committee further reviewed the treatment pathway consistent with the Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment schedule as presented by Llovet et al. (2008). The clinical experts agreed that the BCLC staging system is used in UK clinical practice.

4.3 The committee was aware that the licensed indication for sorafenib is hepatocellular carcinoma without specific restrictions. However, the clinical effectiveness evidence from the SHARP study was for patients with advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable. This population was consistent with UK clinical practice and clinical guidelines as outlined in the company's decision problem. The committee noted that the company presented evidence from SHARP in which patients had predominantly BCLC stage C (that is, advanced stage) disease (82.4%). They also had predominantly good liver function (that is, Child-Pugh grade A liver function; 96.5%), and good Eastern Cooperative Oncology Group (ECOG) performance status (0 to 2). The committee considered how the clinical effectiveness evidence from SHARP related to the total UK population with advanced hepatocellular carcinoma, particularly for patients with Child-Pugh grade B liver function. The committee heard from the clinical experts that systemic therapy with sorafenib would be considered for patients with Child-

Pugh grade B liver function although this type of therapy may be less clinically effective than for patients with Child-Pugh grade A liver function. The committee accepted that patients with advanced hepatocellular carcinoma with either Child-Pugh grade A or B liver function may benefit from systemic therapy, although not necessarily to the same degree. The committee accepted that the company's decision problem focused on advanced hepatocellular carcinoma and was in accordance with the scope.

4.4 The committee then discussed possible comparators used in the UK for advanced hepatocellular carcinoma in clinical practice. The committee accepted that in UK clinical practice, treatment with conventional chemotherapy (such as doxorubicin) would be recommended only for a minority of patients who are able to tolerate it. The committee noted that usual treatment for patients with intermediate hepatocellular carcinoma (defined as asymptomatic tumours without vascular invasion or hepatic spread) is transarterial chemoembolisation, in line with current clinical guidelines. The committee was aware that this subgroup was outside the decision problem presented by the company. Therefore best supportive care was accepted as an appropriate comparator for most patients with advanced hepatocellular carcinoma.

Clinical effectiveness (NICE technology appraisal guidance 189)

4.5 The committee considered the clinical effectiveness data presented by the company. It noted that evidence from the clinical studies of sorafenib plus best supportive care suggested that it increased median survival by more than 2.8 months compared with placebo plus best supportive care. The committee also noted that there was a statistically significant difference in median time to radiological disease progression for patients in the sorafenib group compared with the placebo group. The committee was aware that there was an extension in time to disease progression of 11.7 weeks according to independent assessment or 5.1 weeks according to investigator assessment, compared with placebo. The committee accepted the evidence from SHARP, but was aware that the study was stopped early, potentially underestimating the survival benefit attributable to sorafenib. The committee heard from clinical experts and patient experts that the

observed benefits in overall survival and time to radiological disease progression were clinically meaningful. It noted that a statistically significant difference was not seen for time to symptomatic disease progression for sorafenib compared with placebo. However, the committee accepted the company's and evidence review group's (ERG's) view that the questionnaire used to measure time to symptomatic disease progression (FHSI-8) may not have been able to distinguish between the toxicity of sorafenib, symptoms of the underlying liver disease, and the symptoms of advanced hepatocellular carcinoma.

4.6 The committee heard from a patient expert that severe adverse events (such as diarrhoea and hand-foot skin reaction) had been experienced during 15 months of treatment with sorafenib, and occasionally it was necessary to stop treatment temporarily. The clinical experts confirmed that similar adverse events have been seen in clinical practice, but no patients in their experience had completely stopped treatment with sorafenib for this reason. The patient experts agreed that although the adverse events experienced were unpredictable and affected health-related quality of life, they could be tolerated because of the benefits in terms of extension to life.

4.7 Based on the clinical effectiveness evidence and the testimony from clinical experts and patient experts, the committee concluded that sorafenib is a clinically effective treatment for advanced hepatocellular carcinoma when surgical or locoregional therapy had failed or was not suitable.

Cost effectiveness (NICE technology appraisal guidance 189)

4.8 The committee discussed the cost effectiveness of sorafenib for patients with advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable. The committee noted that the base-case incremental cost-effectiveness ratio (ICER) presented by the company was originally £64,800 per quality-adjusted life year (QALY) gained. When the patient access scheme was included this went down to £51,900 per QALY gained. Both ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources.

4.9 The committee noted that the ICER presented in the company's base case depended on the extrapolation of overall survival beyond the SHARP study timeframe by fitting a log normal probability distribution. Several alternative probability distributions were considered and fitted the data well, and the committee was aware that although the log normal curve provided a slightly better fit, particularly for the early trial data, alternatives also fitted the data well. The main differences were in the shape of the curves at the tail of the distribution where, for example, a Weibull curve with a heavier tail was a good fit. The committee concluded that, although the log normal curve provided a slightly better fit to the observed data, it could not be accepted as the definitive function to extrapolate beyond the study data. The Weibull distribution, which also provided an acceptable fit, should also be considered in any consideration of uncertainty. The base-case log normal extrapolation produced an ICER for sorafenib of £51,900 per QALY gained, which was at the lowest end of the range. The Weibull extrapolation of survival data produced an ICER that was substantially higher (commercial in confidence) than the log normal base case.

4.10 The committee then discussed the ERG's critique of the company's patient access scheme submission. The committee noted concerns about the discrepancies in the dosage of sorafenib and the length of time a pack would last between the patient access scheme as modelled and as described in the summary of product characteristics. It agreed that the description in the summary of product characteristics did not account for dose reductions or stopping treatment temporarily, and that the treatment intensity modelled in the company's submission (based on SHARP) was more appropriate. The committee considered that the cost of post-progression sorafenib treatment was removed from the model but that the benefits were not adjusted. It agreed that, because in clinical practice the benefit from post-progression treatment is likely to be small, retaining the benefits in the model would have a minimal effect on the ICER.

4.11 The committee also noted the inconsistencies in costs associated with treatment duration and agreed that the treatment costs should be based on the actual length of the model cycle. This increased the ICER derived using the log normal extrapolation from £51,900 to £52,600 per QALY gained. It also increased the corresponding (commercial in confidence) ICER using the Weibull extrapolation of survival data. The committee also noted that the company's model did not take into account the administration costs to the NHS of the patient access scheme

but concluded that this would only increase the ICERs marginally.

4.12 The committee was aware of the concerns raised by the ERG about inconsistencies in the utilities used in the company's model. However, it noted that when alternative utility values from a previous renal cell carcinoma assessment report (used to develop NICE's technology appraisal guidance on sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma and bevacizumab [first-line], sorafenib [first- and second-line], sunitinib [second-line] and temsirolimus [first-line] for the treatment of advanced and/or metastatic renal cell carcinoma) were used in a sensitivity analysis, the log normal base-case ICER was not significantly affected.

4.13 The committee considered the additional work by the ERG on the independent and investigator assessments of time to radiological disease progression. It noted that the ICER presented in the company's base case depended on investigator assessment (rather than independent assessment, which was the primary analysis in SHARP). The committee noted that the ERG's analyses demonstrated that the original log normal base case increased to £76,000 per QALY gained (not including the patient access scheme) when using the independent assessment of time to radiological disease progression. The corresponding (commercial in confidence) ICER derived using the Weibull extrapolation of survival data would also be substantially higher. Therefore it concluded that sorafenib, as a treatment for advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable, would not be a cost-effective use of NHS resources.

4.14 The committee then considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

- The treatment is licensed or otherwise indicated for small patient populations.

  In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.15 The committee discussed whether the benefit provided by sorafenib in hepatocellular carcinoma fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It noted from the clinical studies that life expectancy without sorafenib was unlikely to be greater than 24 months and was potentially as low as 7.9 months, although the latter was based on SHARP, which was stopped early. The committee considered that evidence from the clinical studies of sorafenib plus best supportive care suggested that it increased median survival by more than 2.8 months compared with placebo plus best supportive care, and the company's economic model predicted a mean gain in overall survival of 6.1 months, although this depended on the method of extrapolation. Although the committee noted that sorafenib is licensed for indications other than hepatocellular carcinoma, the committee considered sorafenib to fulfil the small population criterion for an end-of life treatment. In summary, the committee was satisfied that sorafenib for advanced hepatocellular carcinoma met the criteria for an appraisal of a life-extending, end-of-life treatment, and that the evidence presented was supported by robust data.

4.16 The committee then discussed the range of cost-effectiveness estimates for sorafenib (with the lowest being the ICER of £52,600 per QALY gained and the highest being substantially greater), in light of the end-of-life considerations. It considered that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great. Therefore the committee concluded that sorafenib as a treatment for advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable would not be a cost-effective use of NHS resources.

4.17 The committee considered whether there were any subgroups of people for whom sorafenib would be considered a cost-effective use of NHS resources. The

committee noted that the subgroups presented by the company were based on a small number of patients, and because the clinical study was not powered to assess differential patient response to treatment, the subgroups were intended to be descriptive only. Also, no adjustments were made for multiple comparisons. The committee was aware that there was limited evidence of clinical effectiveness in these subgroups and that the ICERs would be based on a weak evidence base. Therefore the committee was not satisfied that the estimates of extension to life were robust or that the resulting subgroup ICERs were plausible. It concluded that it would not be appropriate to recommend sorafenib for specific subgroups of patients with advanced hepatocellular carcinoma.

Cancer Drugs Fund reconsideration of NICE technology appraisal guidance 189

4.18 This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on sorafenib for the treatment of advanced hepatocellular carcinoma. At its first reconsideration meeting, the committee considered the company's submission, including:

- a Commercial Medicines Unit price that was lower than the price used in the original appraisal
- data from 2 observational studies:
  - GIDEON, unmatched to the characteristics of the SHARP population, and Palmer et al. (2013), also unmatched to SHARP, which the company used to validate the log normal curve it chose in the original appraisal to extrapolate overall survival beyond the end of SHARP (see section 4.9)
- an estimate of the duration of treatment using data from SHARP on time to disease progression
- the committee's preferred assumptions on costs from the original appraisal (see section 4.11)
- updated unit cost and resource use estimates.

4.19 At its second meeting, the committee considered the company's responses to the appraisal consultation document, including:

- evidence from GIDEON, now matched to the SHARP population for the baseline characteristics of patients that might influence mortality, to validate the log normal curve extrapolating overall survival beyond the end of SHARP
- further explanation about Palmer et al.
- an estimate of the duration of treatment using individual patient data on time to treatment discontinuation from SHARP (the committee's preferred assumption)
- justification for using only recent data on resource use in the economic model
- a cost-effectiveness analysis calculated using a lower Commercial Medicines Unit price of sorafenib than considered at the first meeting.

The committee also considered the ERG's review of the company's submission, the ERG's review of the company's response to the appraisal consultation document and the ERG's exploratory analyses.

4.20 At its third meeting, the committee considered the responses to the appraisal consultation document, including:

- UK audit data from King et al. (2016)
- an estimate of the duration of treatment using individual patient data on time to treatment discontinuation from GIDEON (matched to the SHARP population)
- a cost-effectiveness analysis calculated using a lower Commercial Medicines Unit price of sorafenib than considered at the second meeting.

Population

4.21 The committee noted that SHARP's inclusion criteria specified people with Child-Pugh grade A liver function and an ECOG performance status of 0 to 2, but that a very small proportion of people with Child-Pugh grade B liver function were

enrolled (approximately 3%). The committee noted consultation comments from professional groups that suggested sorafenib may be more clinically effective in people with Child-Pugh grade A liver function and good performance status. It was aware that results from the King et al. study showed median overall survival in people with Child-Pugh grade A liver function was 9.5 months, compared with 4.6 months in people with Child-Pugh grade B liver function and that the Gideon study demonstrated median overall survival of 6.2 months in people with Child-Pugh grade B7 liver function. The committee highlighted that the majority of people contributing data to the observational studies submitted by the company for the Cancer Drugs Fund reconsideration meetings had Child-Pugh grade A liver function. The committee acknowledged the comments from clinical experts and NHS England that current clinical experience suggests that patients need both adequate liver function and performance status to have sorafenib in clinical practice in England. On this basis, they also commented that treatment should be restricted to people with Child-Pugh grade A liver function and performance status of 0 to 2. Taking all the evidence into account, the committee concluded that people with Child-Pugh grade A liver function are the appropriate population for its recommendations for treating advanced hepatocellular carcinoma with sorafenib in England.

Validating the overall survival extrapolation

4.22 The committee understood that the final draft guidance issued during the original appraisal went to an appeal panel. It was aware that the appeal panel concluded that there was opportunity to comment on overall survival modelling and dismissed all appeal points. In the final guidance the committee therefore concluded that the Weibull distribution should be taken into account in any consideration of uncertainty.

4.23 The committee discussed the 3 longitudinal observational studies; Palmer et al., GIDEON and King et al. It recognised that Palmer et al. was a published retrospective cohort study comparing patients with hepatocellular carcinoma in 2 hepatobiliary oncology units in the UK who either received funding for sorafenib (n=57) or did not receive funding (n=76) before the existence of the Cancer Drugs Fund. The committee heard from the company that the decision to fund sorafenib was not based on clinical variables. The committee was aware that

there was a higher proportion of patients with metastatic disease in the unfunded group. The committee noted that patients who did not receive funding for sorafenib did not live as long as patients who did have funding. It also considered that the association between funding and death may be confounded, that is, patients with better prognoses might be more likely to receive funding and treatment than patients with poorer prognoses. It noted the ERG's comment that the study was not suitable for decision-making. However, the committee could not exclude the possibility of residual confounding and concluded that the data from Palmer were a less robust source of evidence than the GIDEON data, now matched to SHARP. It further noted that the parametric curves to extrapolate overall survival using the Palmer data did not favour a log normal or Weibull distribution over the other. The committee then discussed the King et al. audit of mainly Cancer Drugs Fund patients in England, noting that it describes the experience of 448 people with hepatocellular carcinoma who had sorafenib. However, the committee noted that the population did not match that of SHARP because of the higher proportion of patients with Child-Pugh B liver function in King et al. The committee concluded that the matched GIDEON data were more appropriate than Palmer or King et al. for validating the extrapolation of overall survival beyond SHARP.

4.24 The committee discussed the GIDEON data, noting that the company responded to the appraisal consultation document by adjusting the data to match the characteristics of the SHARP population, particularly for risk factors for death. The company chose a propensity score, a method of statistical matching, to do this for baseline characteristics reported across both SHARP and GIDEON. The committee recognised that the ERG considered this statistical approach satisfactory but some baseline characteristics likely to affect the risk of death (such as viral hepatitis) could not be matched because of a lack of reporting. The committee also noted that the matched GIDEON sample (n=895) resulted in longer median overall survival than SHARP. The committee noted that this longer median overall survival was associated with a shorter mean treatment duration and dosage compared with SHARP. The committee considered this relationship seemed counterintuitive (that is, it would have expected a shorter treatment duration and dosage to result in a shorter overall survival), and considered that there may be residual confounding. It concluded that there was some uncertainty around the comparability of the matched GIDEON population and the SHARP population.

4.25 The committee then considered the most appropriate parametric curve to extrapolate overall survival in SHARP to fit the matched GIDEON data, which provided a longer period of follow-up. The company fitted log normal and Weibull curves to the Kaplan–Meier data for the matched GIDEON population and stated that the log normal curve provided a better statistical fit to the observed data than the Weibull curve; the committee agreed with this based on standard statistical criteria using the Bayesian information criterion described in Kass et al. (1995). The committee considered that beyond about 600 days, the Weibull curve fitted the data better than the log normal curve. However, the committee was aware that the uncertainty was greater in the tail of the curve where limited or no data existed. The committee understood from the ERG that the log normal function would overestimate overall survival whereas the Weibull function would underestimate it. Therefore, the ERG advised that both curves should be considered when extrapolating overall survival, and to estimate the ICER for sorafenib compared with best supportive care. The committee acknowledged that it would not use statistical goodness of fit alone to choose the most appropriate survival function. It noted that in general the log normal function used by the company to extrapolate survival beyond SHARP fitted GIDEON better than the Weibull function, but that the Weibull function was still plausible. The committee was also aware that the 3 data sets the company had presented (SHARP, GIDEON, and Palmer et al.) for informing the choice of survival distribution did not conclusively favour 1 single distribution. For example, the Bayesian information criterion statistics provided evidence that the log normal function fitted the data better than the Weibull function in the SHARP analysis based on Kass et al., but this was not considered a statistically strong difference and therefore the committee considered that the Weibull function remained plausible. The committee reiterated that SHARP was among the most robust source of evidence it had seen for sorafenib during the Cancer Drugs Fund reconsideration committee meetings. Therefore, the committee concluded that the true estimate of life expectancy with sorafenib compared with best supportive care was likely to lie between the estimates from the log normal and the Weibull distributions, but agreed it was closer to the log normal estimates than the Weibull estimates.

Duration of treatment

4.26 The committee discussed whether the estimates of treatment duration should come from SHARP (the source of the clinical effectiveness data) or from another source. At its first and second meetings, the committee agreed that the effectiveness and costs should ideally come from the same study; this approach was supported by the ERG and by NHS England. The committee noted that in King et al. people with Child-Pugh grade A liver function did not live as long as people in SHARP (9.5 months compared with 10.7 months). The committee considered that this may have been partly explained by the reduction in treatment duration (3.6 months in King et al. compared with 5.3 months in SHARP) and daily dose (590 mg in King et al. compared with 711 mg in SHARP) between the studies. The committee was also aware that people with Child-Pugh grade A liver function in GIDEON had a median overall survival of 13.6 months and a median treatment duration of 4.1 months, which the committee stated seemed counterintuitive when compared with King et al. and SHARP. The committee appreciated that clinical experience with sorafenib had improved over time and adverse events may now be managed better, partly by shorter duration of treatment. The committee heard from NHS England that patients now have treatment for a shorter period of time than was standard in 2007, trading a sizeable decrease in adverse events for a small drop in effectiveness. But taking all the observational evidence into account, the committee noted it had concerns about the generalisability of these results to the SHARP randomised controlled trial. The committee discussed the company's analysis of the individual patient level data on the time to treatment discontinuation from the matched GIDEON analysis. The committee understood from the company that everyone in GIDEON stopped treatment so the company provided only an unrestricted mean and a Kaplan–Meier analysis (rather than a parametric model). But the committee highlighted that it would have preferred the company to also fit parametric curves to the data because of the differences in the GIDEON and SHARP populations, and the small number of events towards the end of the Kaplan–Meier curves of time to treatment discontinuation, which leads to uncertainty. The committee concluded that data from SHARP should be used to estimate duration of treatment, and the total cost of treatment.

4.27 The committee discussed at its first 2 meetings which data from SHARP best reflected the duration of treatment. It understood that the company and the ERG

preferred different methods; the company preferred time to disease progression as a proxy for duration of treatment, whereas the ERG and the committee preferred the actual data on duration of treatment. The committee acknowledged the debate in the original appraisal about using either investigator assessment or independent assessment of disease progression as a surrogate for time on treatment. The company continued to use time to disease progression for treatment duration in its base-case analysis despite the committee's stated preference in the appraisal consultation document. This was because the company considered that the treatment duration in SHARP was longer than seen in UK clinical practice. The committee understood that the ERG considered that the estimates of mean and median treatment duration reported by the Cancer Drugs Fund, King et al., GIDEON and Palmer et al. were inconclusive and therefore did not support the company's claim that SHARP overestimated the treatment duration of sorafenib in clinical practice. The ERG noted that time to progression based on independent assessment (the primary means of assessment in the SHARP protocol) and treatment duration were similar and also noted the committee's preference in the original appraisal for including treatment costs for patients who had treatment after progression. The committee concluded that treatment duration estimates should be based on data directly reflecting the time on treatment.

4.28 The committee discussed the company's methods for extrapolating time on treatment data from SHARP. The company presented a survival analysis of the time from the date of randomisation to the date of discontinuation of treatment from any cause. To extrapolate beyond the end of the trial, the company applied 5 parametric models: exponential, Gompertz, log logistic, log normal and Weibull, plus a hybrid analysis that the company considered the most robust. The committee understood that the ERG preferred the fully parametric log normal model because a hybrid approach was only appropriate when there was a strong rationale for not using all of the available data to inform the extrapolated curve. The committee stated that the log normal distribution was the best statistical fit of the 5 distributions explored by the company. The committee noted that based on the Kass et al. criteria, the Bayesian information criterion statistics strongly indicated that the log normal distribution was a better fit to the observed data than the Weibull. The committee also heard from the clinical expert that approximately 10% of patients are still having sorafenib treatment at 3 years, which supported using the log normal distribution. The committee concluded that

the company's fully parametric method using the log normal distribution was the most robust estimate of treatment duration.

Cost and resource use estimates

4.29 The committee was aware that the company updated the unit cost data in its reconsideration submission. It was also aware that in clinical practice, the company charges the NHS for a full pack of sorafenib at the start of each treatment cycle. Some patients do not complete the treatment cycle. Therefore the company may have underestimated the cost of treatment in its economic modelling for the first reconsideration meeting. In its response to the appraisal consultation document, the company presented cost-effectiveness results for analyses including the wastage of up to 7 days of treatment. The committee concluded that it was appropriate for the company to use updated unit cost data and account for 7 days of drug wastage because this reflected the price relevant to the NHS.

4.30 The committee was aware that in the original appraisal the company based its estimates of resource use, for example, number of hospitalisations, on the opinion of 4 clinicians. But in this reconsideration, the company provided recent resource use estimates based on the opinion of 3 different clinicians. At the first Cancer Drugs Fund reconsideration meeting the committee noted that the revised resource use data estimates varied widely and therefore it was better to pool the original and revised estimates. In its response to the appraisal consultation document, the company claimed that resource estimates from the original appraisal were no longer accurate because of significant changes in clinical practice. Specifically, patients now had treatment in oncology rather than hepatology clinics and had palliative care in the community. The committee noted that the company did not provide any more evidence in its response to the appraisal consultation document. The committee heard from the ERG that the parameters affecting the ICER most when using the updated resource use estimates compared with the pooled resource use estimates were in the best supportive care group, particularly those for admission and frequency of hospitalisation. Also, the committee understood from the ERG that the ICER was extremely sensitive to changes in these parameters. The committee concluded that the company's revised resource use data were not robust and preferred to

pool the original and revised estimates.

4.31 The company provided information that sorafenib would come off patent in approximately 5 years. The committee discussed the implications of this, but also noted that it had no information on the future price of sorafenib. The committee concluded that it could only take into account the company's current price for sorafenib.

End-of-life considerations

4.32 The committee considered the advice about life-extending treatments in NICE's final Cancer Drugs Fund technology appraisal process and methods. It noted the committee's conclusion in the original appraisal that sorafenib in hepatocellular carcinoma met the end-of-life criteria (see section 4.15). The committee agreed that sorafenib was indicated for patients with a short life expectancy and offered an extension to life of at least 3 months compared with current NHS treatment. The committee concluded that sorafenib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment.

Conclusion

4.33 The committee discussed the most plausible ICER for sorafenib compared with best supportive care for treating advanced hepatocellular carcinoma. It considered that there was still uncertainty associated with extrapolating overall survival from SHARP (see section 4.25). The committee agreed that the most plausible ICER should:

- be based on the ERG's exploratory analyses using the company's fully parametric method (log normal distribution) to estimate treatment duration (see section 4.28)
- account for drug wastage for up to 7 days and
- use the pooled resource use data in the absence of more robust updated resource use data.

The committee was aware that after its third meeting the company proposed a new commercial access agreement to NHS England, and the committee was aware of the revised estimates of cost effectiveness. The committee appreciated that the most plausible ICER was below £50,000 per QALY gained for sorafenib compared with best supportive care (based on the ERG's weighted average results; 75% log normal and 25% Weibull distribution to extrapolate overall survival), including the new Commercial Medicines Unit price and the commercial access agreement (the details of the commercial access agreement are confidential and therefore cannot be published). The committee was aware that the most plausible ICER was within the range normally considered a cost-effective use of NHS resources taking into account the extra weight applied to QALYs at the end of life. The committee recalled its conclusion that patients with grade A Child-Pugh liver function are the appropriate population. The committee concluded that sorafenib could be recommended as an option for use in the NHS only for people with Child-Pugh grade A liver function, and only if the company provides sorafenib within the agreed commercial access arrangement.

Cancer Drugs Fund considerations

4.34 Before the commercial access agreement, which was made after the committee's third meeting, the committee had concluded that sorafenib could not be recommended, and considered if sorafenib could be recommended for use within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee was aware that in considering this, the following criteria must be met:

- The ICERs have plausible potential for satisfying the criteria for routine use.
- It is possible that the uncertainty can be addressed through collecting outcome data from patients treated in the NHS.
- It is possible that the data could inform a subsequent update of the guidance (normally within 24 months).

At its second meeting the committee asked the company whether it wanted to include sorafenib in the Cancer Drugs Fund; sorafenib would be funded while collecting data in the Cancer Drugs Fund. At the third meeting, the committee noted that the company had not submitted a proposal for sorafenib to be included in the Cancer Drugs Fund because the GIDEON data were better than those the Cancer Drugs Fund could collect, and that it would seek a recommendation in routine commissioning.

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hepatocellular carcinoma and the doctor responsible for their care thinks that sorafenib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Bayer have agreed that sorafenib will be available to the NHS with a commercial access agreement which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to access.team@bayer.com.

6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

NICE project team

Each technology appraisal is assigned to a team consisting of an associate director, 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

TA189

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Cancer Drugs Fund reconsideration of TA189

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